

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:

C07D 277/40, A61K 31/425, C07D 417/12, 417/14, 277/28, 277/30, 277/24 (11) International Publication Number:

WO 97/24343

(43) International Publication Date:

10 July 1997 (10.07.97)

(21) International Application Number:

PCT/US96/19131

A1

(22) International Filing Date:

4 December 1996 (04.12.96)

(30) Priority Data:

٥

60/009,433 60/023,209

US 29 December 1995 (29.12.95)

1 August 1996 (01.08.96) US

(71) Applicants: BOEHRINGER INGELHEIM PHARMACEUTI-CALS, INC. [US/US]; 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US). BOEHRINGER INGELHEIM (CANADA) LTD. [CA/CA]; 2100, rue Cunard, Laval, Quebec H7S 2G5 (CA).

(74) Agents: RAYMOND, Robert et al.; Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU. LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHENYL THIAZOLE DERIVATIVES WITH ANTI HERPES VIRUS PROPERTIES

(57) Abstract

This invention relates to methods for inhibiting herpes replication and for treating herpes infection in a mammal by inhibiting the herpes helicaseprimase enzyme complex. This invention also relates to thiazolylphenyl derivatives of formula (G) that inhibit the herpes helicase-primase and to pharmaceutical compositions comprising the thiazolylphenyl derivatives, to methods of using and methods of producing the thiazolylphenyl derivatives. In formula (G), R and Z are as defined in the application where Z is the characterising feature.

$$R \longrightarrow N \longrightarrow Z \qquad (G)$$

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Maiawi Maxico
AU	Australia	GN	Guinea	NE	
BB	Barbados	GR	Greece	NL	Niger Netherlands
BE	Belgium	HU	Hungary	NO	
BF	Burkina Faso	IE	ireland	NZ.	Norway
BG	Bulgaria	IT	Italy	PL	New Zealand
BJ	Benin	JP	Japan	PT	Poland
BR	Brazil	KE	Kenya		Portugal
BY	Belarus	KG	Kyrgystan	RO	Romania
CA	Canada	KP	Democratic People's Republic	RU	Russian Federation
CF	Central African Republic		of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SG	Singapore
CI	Côte d'Ivoire	LI	Liechtenstein	SI	Slovenia
CM	Cameroon	LK	Sri Lanka	SK	Slovakia
CN	China	LR	Liberia	SN	Senegal
CS	Czechoslovskia	LT		SZ	Swaziland
CZ	Czech Republic	LU	Lithuania	TD	Chad
DE	Germany	LV	Luxembourg	TG	Togo
DK	Denmark		Latvia	T.J	Tajikistan
EE	Estonia	MC	Monaco	TT	Trinidad and Tobago
ES	Spain	MD	Republic of Moldova	UA	Ukraine
FI	Finland	MG	Madagascar	UG	Uganda
FR	France	ML	Malj	US	United States of America
GA		MN	Mongolia	UZ	Uzbekistan
UA	Gabon	MR	Mauritania	VN	Vict Nam

PHENYL THIAZOLE DERIVATIVES WITH ANTI HERPES VIRUS PROPERTIES

Technical Field of the Invention

This invention relates to methods for inhibiting herpes replication and for treating herpes infection in a mammal by inhibiting the herpes helicase-primase enzyme complex. In a preferred embodiment,

this invention relates to thiazolylphenyl derivatives that inhibit the herpes helicase-primase. This invention also relates to pharmaceutical compositions comprising the thiazolylphenyl derivatives, to methods of using and producing the thiazolylphenyl derivatives.

Background of the Invention

Herpesviruses inflict a wide range of diseases

20 against humans and animals. For instance, herpes
simplex viruses, types 1 and 2 (HSV-1 and HSV-2),
are responsible for cold sores and genital lesions,
respectively; varicella zoster virus (VZV) causes
chicken pox and shingles; and the human

25 cytomegalovirus (HCMV) is a leading cause of
opportunistic infections in immunosuppressed
individuals.

Herpesviruses are complex double-stranded DNA viruses that encode all the enzymes that directly mediate viral chromosomal replication. Seven DNA replication-associated polypeptides are required for human herpesvirus replication. Six of these seven polypeptides show a high degree of homology

-1-

SUBSTITUTE SHEET (RULE 26)

30

across all studied human herpesviruses. These six polypeptides, when expressed by the virus, constitute a heterodimeric DNA-dependent DNA polymerase, a monomeric single-stranded DNA binding protein, and a heterotrimeric helicase-primase complex. The seventh DNA replication-associated polypeptide does not display sequence or functional conservation and is involved in the initiation of lytic viral replication.

10

15

5

Without the function of each of the seven herpesvirus-specific DNA replication proteins, herpesvirus chromosomal replication will not initiate or propagate. This has been demonstrated in two ways for DNA replication in HSV-1. First, temperature sensitive HSV-1 strains have been developed and the complementation groups within these strains mapped on a one-to-one correspondence to the seven HSV DNA replication genes.

20 Additionally, transient replication assays that utilized recombinant DNA plasmids containing single DNA replication genes have found that the presence of each of the seven genes was required for the efficient replication of a tester plasmid containing an HSV-1 origin of DNA replication.

More recently, the DNA replication genes in other herpesviruses (i.e., Epstein-Barr virus, cytomegalovirus and varicella zoster virus) have been delineated. These gene sequences were identified as homologous to the HSV-1 DNA replication genes. Furthermore, transient replication assays containing either an Epstein-Barr virus or cytomegalovirus lytic origin of DNA

replication confirmed their identity. In varicella zoster virus (the human herpesvirus most closely related to HSV-1) DNA replication genes were found to be highly homologous to HSV-1 (>50% at the amino acid level) and present at identical relative locations on the two viral chromosomes. Although no follow-up analysis on varicella zoster virus DNA replication genes has been presented to date, it is highly unlikely that differences in the varicella zoster virus and HSV-1 DNA replication programs exist.

From the above, it is clear that human DNA replication proteins are unable to substitute for the HSV-1 encoded enzymes. Otherwise, temperature-sensitive viral polypeptides would have been complemented by human counterparts and the defective viruses would have continued to grow and replicate, even at elevated temperatures.

- 20 Similarly, in transient replication assays, if human proteins were capable of complementing any of the seven herpesvirus-encoded polypeptides, an absolute dependence on the presence of each of these herpesvirus DNA replication-specific genes
- 25 would not have been observed. Therefore, inhibiting the activity of those virally-encoded proteins represents an effective way of preventing herpesviral replication.
- 30 The helicase-primase enzyme occupies a key and critical place in the herpesvirus DNA replication program. The observation that the genes encoding the herpes helicase-primase are not only essential for replication, but are also highly conserved

- 3 -

across the range of known herpesviruses underscores the importance of this enzyme in mediating viral chromosomal replication.

- In the helicase-primase complex, two of the three polypeptides (e.g., the expression products of the UL5 and UL52 genes of HSV-1) promote catalysis of duplex DNA unwinding and RNA primer biosynthesis. The third polypeptide, encoded by the UL8 gene,
- appears to modulate primase activity. The assembled helicase-primase enzyme complex functions both in the initiation and propagation stages of herpesvirus DNA replication. It is responsible for the synthesis of RNA primers necessary for the
- initiation of all new DNA synthesis by the herpesvirus DNA polymerase. Additionally, for DNA replication to proceed, duplex viral chromosomal DNA must first be unwound to the single-stranded replicative intermediate because the herpesvirus
- DNA polymerase is inactive on fully duplex DNA.

 The helicase-primase is also responsible for this important DNA unwinding event.
- Conventional anti-herpes therapies have not focused on inhibiting the activity of the herpes helicase-primase(see R.E. Boehme et al., Annual Reports in Medicinal Chemistry, 1995, 30, 139). The most widely used anti-herpes agents to date are purine and pyrimidine nucleoside analogs, such as
 - acyclovir and ganciclovir. These nucleoside analogues inhibit replication of viral DNA by their incorporation into a growing DNA strand. The nucleoside analogue-based inhibitors of HSV-1 growth have found only limited success and are not

generally useful in treating recurring infections in the majority of patients. In addition, the infection of humans by other herpesviruses, such as varicella zoster virus or cytomegalovirus, show little or no responsiveness to nucleoside-based therapies.

The lack of broad spectrum anti-herpesvirus activity by the nucleoside-based therapies is not 10 surprising because these compounds act by indirect biological mechanisms. Nucleoside analogues must first be activated to the nucleoside monophosphate by a virally-encoded thymidine kinase enzyme. should be pointed out that only HSV and varicella 15 zoster virus encode thymidine kinase enzymes. may, in part, explain the inability to adapt nucleoside-based therapies to the treatment of other human herpesviruses. After initial phosphorylation, the nucleoside analogue 20 monophosphate must be further phosphorylated to the triphosphate by human-encoded enzymes prior to its action. Ultimately, the triphosphorylated nucleoside analogue is incorporated into a nascent DNA chain during viral genomic replication, thereby 25 inhibiting the elongation of that DNA chain by the herpes DNA polymerase.

The final incorporation step of the nucleoside-based therapies has been characterized as "competitive"

30 because the herpes DNA polymerase does not display a preference for the activated nucleoside drug versus normal deoxynucleoside triphosphates. However, because the action of the DNA polymerase is not considered rate-limiting for herpesvirus DNA

- 5 -

replication, the utility of nucleoside-derived compounds in treating herpesvirus infections is necessarily limited. Accordingly, the need for effective, safe therapeutic agents for treating herpesvirus infections continues to exist.

Summary of the Invention

5

The invention described herein overcomes the above-10 mentioned limitations and satisfies the abovementioned needs by providing non-nucleoside-based inhibitors that act directly in interfering with the likely rate-limiting process in herpesvirus DNA replication: the action of the helicase-primase 15 enzyme. Furthermore, since the herpesvirus helicase-primase enzyme is conserved across the human herpesviruses, compounds of this invention are effective against the full spectrum of herpesviruses, including HSV, varicella zoster 20 virus and cytomegalovirus, and also against nucleoside-nonresponsive and nucleoside-resistant herpes infections.

One objective of this invention is to provide

25 methods for inhibiting a herpes helicase-primase,
for inhibiting replication of a herpesvirus and for
treating herpes infection in a mammal using a nonnucleoside compound characterized by:

- (a) an ability to inhibit DNA-dependent NTPase30 activity of the herpes helicase-primase;
 - (b) an ability to stabilize the interaction between the herpes helicase-primase and a DNA substrate;

- (c) an inability to inhibit DNA-independent NTPase activity of the herpes helicase-primase;
- (d) an inability to bind directly to double-stranded DNA; and
- 5 (e) an inability to inhibit the herpes origin binding protein helicase encoded by the UL9 gene of HSV.
- A further objective of this invention is to provide 10 thiazolylphenyl derivatives useful in the methods of this invention and pharmaceutical compositions comprising those thiazolylphenyl derivatives.
- Another objective of this invention is to provide 15 processes for preparing the thiazolylphenyl derivatives of this invention.

Yet another objective of this invention is to provide a method for identifying non-nucleoside

20 herpes helicase-primase inhibitors by screening for (1)inhibition of single-stranded DNA-dependent NTPase activity and (2) lack of inhibition of DNA-independent NTPase activity of a herpes helicase-primase.

25

A further objective of this invention is to provide non-nucleoside herpes helicase-primase inhibitors identified using the methods of this invention.

- 30 Yet a further objective of this invention is to provide non-nucleoside herpes helicase-primase inhibitors characterized by:
 - (a) an ability to inhibit DNA-dependent NTPase activity of the herpes helicase-primase;

(b) an ability to stabilize the interaction between the herpes helicase-primase and a DNA substrate;

- (c) an ability to inhibit replication of a herpesvirus in cell culture by at least about 50% at a concentration of less than about 500 nM;
 - (d) an inability to inhibit DNA-independent NTPase activity of the herpes helicase-primase;
- (e) an inability to bind directly to doublestranded DNA; and
- (f) an inability to inhibit the herpes origin binding protein helicase encoded by the UL9 gene of HSV-1.
- 15 Still a further objective of this invention is to provide pharmaceutical compositions containing the non-nucleoside inhibitors of this invention and methods for treating herpes infection in a mammal using those pharmaceutical compositions.

20

5

10

Description of the Drawings

Figure 1 graphically illustrates the therapeutic effect of acyclovir and a thiazolylphenyl derivative of Group 1 (described hereinafter) against an acyclovir-resistant HSV infection in an immunodeficient mouse model. The HSV strain in this instance is HSV-1 PAAr5.

30

Figure 2 shows a dose response curve for a thiazolylphenyl derivative of Group 1 against the acyclovir-resistant HSV-1 strain, noted for Figure 1, in the same mouse model.

Figure 3 graphically illustrates the therapeutic effect of acyclovir and a thiazolylphenyl derivative of Group 1 against an acyclovir-resistant HSV infection in the immunodeficient mouse model. The HSV strain in this instance is HSV-1 dlsptk.

Figure 4 shows a dose-response curve of a

10 thiazolylphenyl derivative of Group 1 against the
acyclovir-resistant strain noted for Figure 3, in
the same mouse model.

Figure 5 graphically illustrates the ability of two
15 thiazolylphenyl derivatives of Group 1 to stabilize
the interaction between the herpes HSV-1 helicaseprimase and a DNA substrate.

Detailed Description of the Invention

20

As used herein, the following definitions apply unless otherwise noted:

With reference to the instances where (R) or (S) is used to designate the configuration of a radical, e.g. R⁴ of the compound of formula 1, the designation is done in the context of the compound and not in the context of the radical alone.

30 The term "halo" as used herein means a halo radical selected from bromo, chloro, fluoro or iodo.

The term "herpes" as used herein refers to any virus in the herpes family of viruses and particularly, to

-9-

SUBSTITUTE SHEET (RULE 26)

those herpesviruses that encode a herpes helicaseprimase homologous to the herpes helicase-primase of HSV-1. The herpes family of viruses includes, but is not limited to, HSV-1, HSV-2, cytomegalovirus, varicella zoster virus and Epstein-Barr virus.

The term "lower alkanoyl" as used herein, either alone or in combination with another radical, means a straight chain 1-oxoalkyl containing from one to six carbon atoms or a branched chain 1-oxoalkyl containing from four to six carbon atoms; for example, acetyl, propionyl(1-oxopropyl), 2-methyl-1-oxopropyl, 2-methylpropionyl and 2-ethylbutyryl. Note that the term "lower alkanoyl" when used in combination with "lower cycloalkyl" would include "(lower cycloalkyl)carbonyl".

The term "(1-3C)alkyl" as used herein, either alone or in combination with another radical, means alkyl radicals containing from one to three carbon atoms and includes methyl, ethyl, propyl and 1-methylethyl.

The term "lower alkyl" as used herein, either alone or in combination with another radical, means straight chain alkyl radicals containing one to four carbon atoms and branched chain alkyl radicals containing three to four carbon atoms and includes methyl, ethyl, propyl, butyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl and 2,2-dimethylpropyl.

The term "(1-8C)alkyl" as used herein means straight and branched chain alkyl radicals containing from

5

one to eight carbon atoms and includes ethyl, butyl, 1-methylpropyl, 1-ethylpropyl, 2,2-dimethylpropyl, 1-ethylbutyl, 2-ethyl-2-methylbutyl, 2-ethylbutyl, 1-propylbutyl, 2-propylpentyl and the like.

5

10

15

25

The term "lower alkenyl" as used herein means an aliphatic hydrocarbon containing two to four carbon atoms and one double bond and includes ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl and 3-butenyl.

The term "lower alkynyl" as used herein means an aliphatic hydrocarbon containing two to four carbon atoms and one triple bond and includes ethynyl, 1-propynyl, 2-propynyl and 1-butynyl.

The term "{1-(lower alkyl)-(lower cycloalkyl)}" as used herein means a lower cycloalkyl radical bearing a lower alkyl substituent at position 1; for example, 1-ethylcyclopropyl, 1-propylcyclopentyl and 1-propylcyclohexyl.

The term "lower cycloalkyl" as used herein, either alone or in combination with another radical, means saturated cyclic hydrocarbon radicals containing from three to seven carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

30 The term "lower alkoxy" as used herein means straight chain alkoxy radicals containing one to four carbon atoms and branched chain alkoxy radicals containing three to four carbon atoms and includes methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy and

- 11 -

1,1-dimethylethoxy. The latter radical is known commonly as tert-butoxy.

- The term "amino" as used herein means an amino radical of formula -NH2. The term "lower alkylamino" as used herein means alkylamino radicals containing one to six carbon atoms and includes methylamino, propylamino, (1-methylethyl)amino and (2-methylbutyl)amino. The term "di(lower
- alkyl) amino "means an amino radical having two lower alkyl substituents each of which contains one to six carbon atoms and includes dimethylamino, diethylamino, ethylmethylamino and the like.
- The term "Het" as used herein means a monovalent radical derived by removal of a hydrogen from a five- or six-membered saturated or unsaturated heterocycle containing from one to two heteroatoms selected from nitrogen, oxygen and sulfur.
- Optionally, the heterocycle may bear one or two substituents; for example, N-oxido, lower alkyl, phenyl-(1-3C)alkyl, lower alkoxy, halo, amino or lower alkylamino. Examples of suitable heterocycles and optionally substituted heterocycles include
- pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, 1H-imidazole, 1-methyl-1H-imidazole, pyrazole, furan, thiophene, oxazole, isoxazole, thiazole, 2methylthiazole, 2-aminothiazole, 2-(methylamino)thiazole, piperidine, 1-methylpiperidine, 1-
- methylpiperazine, 1,4-dioxane, morpholine, pyridine, pyridine N-oxide, pyrimidine, 2,4-dihydroxypyrimidine and 2,4-dimethylpyrimidine.

5

10

The term "pharmaceutically acceptable carrier" or "veterinarily acceptable carrier" as used herein means a non-toxic, generally inert vehicle for the active ingredient which does not adversely affect the ingredient.

The term "effective amount" means a predetermined antiviral amount of the antiviral agent, i.e. an amount of the agent sufficient to be effective against the virus in vivo.

The term "inhibit", when used in connection with enzymatic activity, refers generally to inhibiting the enzymatic activity by at least about 50% at a 15 concentration of about 100 µM (and preferably at a concentration of about 50 µM, more preferably, at a concentration of about 25 µM, even more preferably, at a concentration of about 10 µM and most preferably, at a concentration of about 5 µM or 20 less) in a conventional in vitro assay for enzymatic inhibition. In contrast, the term "inability to inhibit" refers generally to inhibiting enzymatic activity by no more than about 50% at concentration of about 100 µM. For example, a compound with an 25 HSV-1 helicase-primase IC₅₀ value of 1.5 μM inhibits HSV-1 helicase-primase activity by 50% at a concentration of 1.5 µM. Therefore, this compound is an HSV-1 helicase-primase inhibitor, as the term is used herein. However, a compound having an IC50 30 value of 150 μM inhibits enzymatic activity by 50% at a concentration of 150 µM and therefore, is not considered an inhibitor of that enzyme.

- 13 -

The term "bind directly to DNA" refers to the ability of a compound to bind to DNA in the absence of added enzyme. It should be understood that the compounds of this invention might bind to DNA when enzyme is present. However, these compounds do not bind to DNA in the absence of enzyme. The ability of a compound to bind directly to DNA is preferably ascertained by UV/VIS spectroscopy. Alternatively, fluorescence or circular dichroism may be used. Each of these techniques is well known and may be carried out using methodology familiar to those of ordinary skill in the art.

In one embodiment, the present invention refers to

methods for inhibiting a herpes helicase-primase by
stabilizing the interaction between the herpes
helicase-primase and its viral DNA substrate.
Directly-acting non-nucleoside herpes helicaseprimase inhibitors have been identified using the

methods of this invention. It has also been
established for the first time that effectors of the
herpesvirus helicase-primase capable of stabilizing
the enzyme complex's interaction with its DNA
substrate are capable of directly inhibiting herpes

helicase-primase activity.

Without wishing to be bound by theory, it is believed that preferred compounds of this invention bind to an allosteric effector site located on the UL5 or the UL52 subunit of HSV-1 helicase-primase (and homologous regions of other herpesvirus helicase primase enzymes), thereby causing the enzyme to bind more tightly to the DNA substrate. This "stabilization" inhibits enzymatic activity by

10

30

070404044

impeding enzymatic progression along the DNA substrate. It is likely that a particularly favorable binding site for enzymatic inhibition is an allosteric effector site located within the A-B sequence of the UL52 subunit. More specifically, it is believed that the inhibitory action of these compounds is mediated by a terminal "zinc finger" motif on one of the herpes helicase-primase's catalytic subunits.

10

30

5

Compounds useful for inhibiting a herpes helicaseprimase according to the above mechanism may be readily identified by assaying a test compound's ability to inhibit enzyme-associated single-stranded 15 DNA-dependent NTPase activity of a herpes helicaseprimase (such as the helicase-primase of HSV-1). Such a screening method may advantageously be established for use as a high throughput screen (HTS). An HTS based upon this methodology is 20 typically easier to run and requires less enzyme than other assays, such as the helicase-driven solid phase unwinding assay. Additionally, the enzyme used for the DNA-dependent NTPase assay need not be as pure or used in as great an amount as in the 25 helicase assay.

Compounds active in the HTS may be further assayed to determine their herpes helicase-primase binding specificity. Although the following assays are described in one particular sequence, it should be understood that not all of these assays need to be performed for successful identification of herpes helicase-primase inhibitors. In addition, the exact order of assays may be altered, if desired. These

- 15 -

and other procedural options can be considered by those of ordinary skill in the art.

One additional assay that may be run determines the ability of test compounds to inhibit helicase-primase-associated DNA-independent NTPase activity. The compounds useful in this invention do not inhibit this activity, whereas competitively-acting nucleoside analogues do inhibit this activity.

10

15

5

Other assays measure a test compound's ability to inhibit enzyme-mediated RNA primer biosynthesis and stabilize the interaction between the helicase-primase and its DNA substrate. Compounds useful in this invention do not inhibit DNA-independent NTPase activity and do not intercalate into, nor otherwise bind directly to, double-stranded DNA. These activities are also readily measurable by assays known to those of ordinary skill in the art.

20

25

30

Assays designed to measure helicase activity of the herpes helicase-primase in solution may also be performed. Compounds which inhibit helicase activity in that assay can then be counter screened for activity against other eukaryotic helicases, such as the HSV-1 origin binding protein helicase encoded by the UL9 HSV-1 DNA replication specific gene. These origin binding protein-driven DNA unwinding assays are stimulated by the addition of an equimolar amount of the HSV-1 single-stranded DNA binding protein. Compounds displaying less than about 10-fold specificity for the helicase-primase (e.g., IC₅₀ (origin binding protein helicase activity)<10 X IC₅₀ (helicase-primase helicase

activity)) should be excluded as likely non-specific helicase inhibitors. Other identified prokaryotic or eukaryotic helicases could also be used for determining compound specificity.

5

10

15

20

25

30

Another assay measures the ability of a test compound to stabilize the interaction between the helicase-primase and DNA substrates (e.g., those that are naturally occurring, or those designed to mimic either replication fork-like structures or primase recognition sequences). The term "DNA substrate" as used in this context refers to duplex DNA which, in the presence of a herpes helicaseprimase, is susceptible to enzymatic activity. It will be appreciated that any sequence of doublestranded DNA which is unwound by a herpes helicaseprimase may be used in assays to test the ability of a test compound to stabilize the interaction between the helicase-primase and DNA. Such an assay may be performed by binding the helicase-primase enzyme to a fluorescently labeled DNA substrate, for example, a DNA substrate designed to model a replication fork-like structure or primase consensus binding site. Fluorescence anisotropy may then be used to directly determine the fraction of enzyme bound to target nucleic acid substrates by increasing salt concentrations to fractionally depopulate the enzyme from the DNA target sequence. Addition of stabilizing inhibitors shifts the equilibrium from free (in solution) to bound (to DNA).

- 17 -

A preferred method for identifying a non-nucleoside herpes helicase-primase inhibitor according to this invention comprises the steps of:

- (a) measuring the ability of the test compound to inhibit DNA-dependent NTPase activity of the herpes helicase-primase; and
- (b) measuring the ability of the test compound to inhibit DNA-independent NTPase activity.
- In this preferred method, herpes helicase-primase inhibitors according to this invention inhibit DNA-dependent NTPase activity, but do not inhibit DNA-independent NTPase activity.
- This invention also envisions various methods for inhibiting a herpes helicase-primase and inhibiting replication of a herpesvirus. According to a preferred embodiment, these methods comprise the step of contacting the helicase primase with a non-nucleoside compound characterized by:
 - (a) an ability to inhibit DNA-dependent NTPase activity of the herpes helicase-primase;
 - (b) an ability to stabilize the interaction between the herpes helicase-primase and a DNA substrate;
 - (c) an inability to inhibit DNA-independent NTPase activity of the herpes helicase-primase;
 - (d) an inability to bind directly to doublestranded DNA; and
- 30 (e) an inability to inhibit the herpes origin binding protein helicase encoded by the UL9 gene of HSV-1.

5

25

25

30

This invention also includes various methods for treating herpes infection in a mammal. In a preferred embodiment that method comprises the step of administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically acceptable carrier and a non-nucleoside compound characterized by:

- (a) an ability to inhibit DNA-dependent NTPase 10 activity of the herpes helicase-primase;
 - (b) an ability to stabilize the interaction between the herpes helicase-primase and a DNA substrate:
- (c) an inability to inhibit DNA-independent NTPase activity of the herpes helicase-primase;
 - (d) an inability to bind directly to doublestranded DNA; and
- (e) an inability to inhibit the herpes origin binding protein helicase encoded by the UL9 gene of 20 HSV-1.

In all of the above-methods, the non-nucleoside compound is preferably further characterized by an ability to inhibit herpes helicase-primase mediated RNA primer biosynthesis. In addition, preferred non-nucleoside inhibitors of this invention are further characterized by an ability to inhibit replication of a herpesvirus in cell culture by at least about 50% at a concentration of less than about 5 µM (more preferably, less than about 2 µM, even more preferably, less than about 1 µM or less than about 500 nM and most preferably, less than about 100 nM). Non-nucleoside compounds of this invention that inhibit replication of a herpesvirus

in cell culture by at least about 50% at a concentration of less than about 50 nM (or more preferably, less than about 10 nM and most preferably, less than about 1 nM) are particularly preferred. It is important to recognize that the compounds, compositions and methods of this invention may be used against nucleoside nonresponsive and nucleoside resistant herpes infections.

10

Using the above noted screening methodologies, a class of thiazolylphenyl derivatives was identified as inhibitors of herpes helicase-primase. These derivatives share the general structure of formula

15 G:

$$R \xrightarrow{N} \int_{S}^{Z} (G)$$

wherein R is selected from the group consisting of hydrogen, lower alkyl, amino, lower alkylamino, 20 di(lower alkyl)amino, lower alkanoylamino, (lower alkoxycarbonyl)amino, di(lower alkoxycarbonyl)amino, ((lower alkylamino)carbonyl)amino and pyridinylamino; and some preferred definitions for Z are detailed herein.

25

More particularly, a thiazolylphenyl derivative of this invention is a compound selected from one of the following groups:

30 Group 1 Compounds: A thiazolylphenyl derivative of formula G wherein R is as defined hereinabove, and

Z is $NR^2-C(0)-O-CH(R^3)-NR^4R^5$ wherein R² is hydrogen or lower alkyl; O is absent (i.e. a valance bond) or methylene; R3 is hydrogen, lower alkyl, phenyl(lower alkyl) or phenyl (lower alkyl) monosubstituted on the aromatic 5 portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; R4 is hydrogen, (1-8C)alkyl, {di(lower alkyl)amino}-(lower alkyl), phenyl(lower)alkyl, phenyl(lower)alkyl monosubstituted or disubstituted 10 on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; 1-indanyl, 2indanyl, (lower cycloalkyl)-(lower alkyl), (Het)-(lower alkyl) wherein Het represents an unsubstituted, monosubstituted or disubstituted five 15 or six membered, monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently from the group consisting of halo, hydroxy, lower alkoxy and lower 20 alkyl; or R3 and R4 together form a - (CH2)m-W- group wherein m is the integer 2 or 3 and W is methylene or carbonyl, W being linked to the nitrogen atom 25 bearing R⁵; and R⁵ is (1-8C)alkyl, phenyl(lower alkyl), phenyl-

R⁵ is (1-8C)alkyl, phenyl(lower alkyl), phenyl (lower alkyl) monosubstituted on the aromatic
 portion thereof with a halo, hydroxy, lower alkoxy
 or lower alkyl; 1-indanyl, 2-indanyl, (lower
30 cycloalkyl)-(lower alkyl), (Het)-(lower alkyl)

wherein Het is as defined hereinbefore,

phenylsulfonyl, 1- or 2-naphthylsulphonyl, 5
(dimethylamino)-1-naphthylsulfonyl, (lower alkylamino)sulfonyl, {di(lower alkyl)amino}sulfonyl,

(Het)-sulfonyl wherein Het is as defined
hereinbefore, lower alkanoyl, (lower cycloalkyl)(lower alkanoyl), {1-(lower alkyl)-(lower
cycloalkyl)}carbonyl, (lower alkoxy)carbonyl,

- phenyl-Y- $(CH_2)_nC(O)$ wherein Y is oxy(-O-) or thio (-S-) and n is 0, 1 or 2 when Y is oxy or n is 1 or 2 when Y is thio, monosubstituted or disubstituted phenyl-Y- $(CH_2)_2C(O)$ wherein Y and n are as defined hereinbefore and the monosubstitution or
- disubstitution occurs on the phenyl portion thereof with a substituent selected from the group consisting of halo, hydroxy, lower alkoxy and lower alkyl; phenyl(lower alkanoyl), phenyl(lower alkanoyl) monosubstituted or disubstituted on the
- phenyl portion thereof with a substituent selected independently from the group consisting of azido, halo, hydroxy, lower alkoxy and lower alkyl; (Het)-(CH₂)_nC(O) wherein Het and n are as defined hereinbefore, (Het)-Y-(CH₂)_nC(O) wherein Het, Y and
- n are as defined hereinbefore, 2-{(lower alkoxycarbonyl)amino}-1-oxoethyl, (lower alkylamino)carbonyl, {di(lower alkyl)amino}carbonyl or (lower alkylamino)thiocarbonyl; or a therapeutically acceptable acid addition salt
- 25 thereof; or

Group 2 Compounds: A thiazolylphenyl derivative of formula G wherein R is as defined hereinbefore, and Z is $NR^{2A}C(O)-A-NR^{3A}R^{4A}$ wherein

30 R^{2A} is hydrogen or lower alkyl;
A is absent or carbonyl;
R^{3A} is hydrogen, (1-8C)alkyl, 2-hydroxyethyl, 3-hydroxypropyl, (1-3C)alkyl monosubstituted with cyano, phenyl(lower alkyl), phenyl(lower alkyl)

monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, di(lower alkyl)amino, lower alkoxy or lower alkyl; (lower cycloalkyl) - (lower alkyl), or (Het) - (lower alkyl) wherein Het represents an unsubstituted, monosubstituted or disubstituted five or six membered, monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is 10 selected independently from the group consisting of halo, hydroxy, lower alkoxy and lower alkyl; and R^{4A} is (1-8C)alkyl, phenyl(lower alkyl), phenyl-(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, 15 di(lower alkyl)amino, lower alkoxy or lower alkyl; 1-indanyl, 2-indanyl, phenyl(lower alkyl) monosubstituted on the aliphatic portion thereof with a hydroxy; (lower cycloalkyl)-(lower alkyl), Het as defined hereinbefore, (Het)-(lower alkyl) 20 wherein Het is as defined hereinbefore or 3-1Hindolylmethyl; or R3A and R4A together with the nitrogen to which they are attached form an unsubstituted, monosubstituted or disubstituted five or six membered, 25 monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently from the group consisting of halo, hydroxy, lower alkoxy and lower alkyl;

- 23 -

or R^{3A} and R^{4A} independently are:

30

wherein L is carbon, oxygen or nitrogen, with the proviso that when L is oxygen, one of R^{6A} or R^{7A} is absent; R^{5A} and R^{6A} are independently selected from the group defined for R^{3A} herein; and R^{7A} is independently selected from the group defined for R^{4A} herein; or therapeutically acceptable acid addition salt thereof; or

- 10 Group 3 Compounds: A thiazolylphenyl derivative of formula G wherein R is as defined hereinbefore and Z is C(O)-NR^{2B}R^{3B} wherein
- R^{2B} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, phenyl(lower alkyl), phenyl(lower alkyl)
- monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy, lower alkyl or trifluoromethoxy; lower cycloalkyl, (lower cycloalkyl)-(lower alkyl), {1-hydroxy-(lower cycloalkyl)-(lower alkyl) or (Het)-(lower alkyl)
- wherein Het represents an unsubstituted,
 monosubstituted or disubstituted five or six
 membered, monovalent heterocyclic ring containing
 one or two heteroatoms selected from the group
 consisting of N, O or S, wherein each substituent is
- 25 selected independently from the group consisting of halo, hydroxy, lower alkoxy and lower alkyl;2benzimidazolylmethyl; and

R^{3B} is lower alkyl, phenyl(lower alkyl),

phenyl(lower alkyl) monosubstituted or disubstituted 30 on the aromatic portion thereof with a halo, hydroxy, lower alkoxy, lower alkyl or trifluoromethoxy; 1-indanyl, 2-indanyl, lower
cycloalkyl, (lower cycloalkyl)-(lower alkyl), {1hydroxy-(lower cycloalkyl)}-(lower alkyl) or (Het)(lower alkyl) wherein Het is as defined
bereinbefore;

or R^{3B} is:

wherein R4B is hydrogen, lower alkyl, phenyl(lower alkyl), phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a 10 halo, hydroxy, lower alkoxy, lower alkyl or trifluoromethoxy; (lower cycloalkyl)-(lower alkyl) or (Het)-(lower alkyl) wherein Het is as defined hereinbefore: R5B has the same significance as R2B hereinbefore and R6B has the same significance as 15 defined for R3B hereinbefore; or R3B is $(CH_2)_{t}NR^{5B}R^{6B}$ wherein t is 1 or 2 and R^{5B} and R^{6B} are as defined hereinbefore; or R3B is CH(R7)CH2OH wherein R^{7B} has the same significance as R^{4B} herein; or R2B and R3B together with the nitrogen to which they are attached form an unsubstituted, monosubstituted or disubstituted five or six membered. monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, 25 O or S, wherein each substituent is selected independently from the group consisting of halo, hydroxy, lower alkoxy, lower alkyl, phenyl (lower alkyl) and phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a 30 halo, hydroxy, lower alkoxy or lower alkyl; with the proviso that when R is (lower alkoxycarbonyl)amino

- 25 -

SUBSTITUTE SHEET (RULE 26)

then R^{2B} is hydrogen; or a therapeutically acceptable acid addition salt thereof; or

Group 4 Compounds: A thiazolylphenyl derivative of formula G wherein R is as defined hereinbefore, and 5 Z is OCH₂C(O)NR^{2C}R^{3C} wherein ${\bf R}^{\rm 2C}$ and ${\bf R}^{\rm 3C}$ are independently hydrogen, lower alkyl, phenyl, phenyl(lower alkyl), phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic 10 portion thereof with a substituent selected independently from the group consisting of halo, hydroxy, lower alkoxy or lower alkyl; 1-indanyl, diphenylmethyl, lower cycloalkyl, (lower cycloalkyl) - (lower alkyl) or (Het) - (lower alkyl) 15 wherein Het represents an unsubstituted, monosubstituted or disubstituted five or six membered, monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently from the group consisting of 20 halo, hydroxy, lower alkoxy and lower alkyl; with the provisos (a) that R^{2C} and R^{3C} cannot both be hydrogen, (b) that when R is hydrogen, methyl or dimethylamino then R^{2C} and R^{3C} cannot both be phenylmethyl, and (c) that when R is amino, then R^{2C} 25 and R3C cannot be the combination of hydrogen and 1,1-dimethylethyl or the combination of methyl and phenyl; or a therapeutically acceptable acid addition salt thereof; or

30

Group 5 Compounds: A thiazolylphenyl derivative of formula G wherein R is as defined hereinbefore, and Z is $CH_2CH_2N(\mathbb{R}^{2D})-C(0)\mathbb{R}^{3D}$ wherein \mathbb{R}^{2D} is hydrogen, lower alkyl, phenyl(lower alkyl), phenyl(lower

alkyl) monosubstituted or disubstituted on aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; (lower cycloalkyl)-(lower (Het) - (lower alkyl), or alkyl) wherein represents an unsubstituted, monosubstituted disubstituted five six membered, or heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently 10 from the group consisting of halo, hydroxy, lower alkoxy and lower alkyl; and

R3D is lower alkyl, lower alkyl monosubstituted, disubstituted or trisubstituted with a halo; phenyl unsubstituted, monosubstituted or disubstituted with 15 hydroxy, lower alkoxy or a halo, lower phenyl(lower alkyl) unsubstituted, monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; 20 lower cycloalkyl, (lower cycloalkyl) - (lower alkyl), Het wherein Het is as defined hereinbefore, (Het)-(lower alkyl) wherein Het is defined hereinbefore; lower alkylamino, di(lower alkvl)amino, or phenyl(lower alkyl)amino unsubstituted, 25 monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; or a therapeutically acceptable acid addition salt thereof.

With reference to greater detail, the five groups of thiazolylphenyl derivatives are described as follows:

- 27 -

Group 1: N-(Thiazolylphenyl)alkanamide Derivatives

According to one embodiment, the present application refers to Group 1 N-(thiazolylphenyl)alkanamide derivatives having antiherpes activity. The selective action of these compounds against these viruses, combined with a wide margin of safety, renders the compounds as desirable agents for combating herpes infections.

10

15

5

These N-(thiazolylphenyl)alkanamide derivatives can be characterized structurally by the presence of a N-{4-(4-thiazolyl)phenyl}amido moiety. Compounds possessing such a moiety have been reported previously, for example:

K.D.Hargrave et al., J. Med. Chem., 1983, 26,

1158; C.G. Caldwell et al., US patent 4,746,669,

20 issued May 24, 1988:

A. Bernat et al., Canadian patent application 2,046,883, published June 30, 1991;

A. Wissner, European patent application 458,037, published November 27, 1991;

J.E. Macor and J.T. Nowakowski, PCT patent application WO 93/18032, published September 16, 1993; and

D.I.C. Scopes et al., UK patent application 2 276 164, published September 21, 1994.

30

The present N-(thiazolylphenyl)alkanamide derivatives can be distinguished readily from the prior art compounds in that they possess different chemical structures and biological activities.

The Group 1 N-(thiazolylphenyl)alkanamide derivatives of this invention can also be represented by formula 1

5

wherein R^1 has the same meaning as R as defined hereinbefore and R^2 , Q, R^3 , R^4 and R^5 are as defined hereinbefore.

- 10 A preferred set of Group 1 compounds of this invention is represented by Group 1-formula 1 wherein R¹ is selected from the group consisting of hydrogen, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, (lower
- alkoxycarbonyl)amino and {(lower alkylamino)carbonyl)amino; R² is hydrogen, methyl or ethyl; Q is absent or methylene; R³ is hydrogen, lower alkyl, phenylmethyl or phenylmethyl substituted on the 4 position of the phenyl ring
- with halo, lower alkoxyl or lower alkyl; R⁴ is hydrogen, (1-8C)alkyl, {di(lower alkyl)amino}-(lower alkyl), phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted on the aromatic portion thereof with halo, hydroxy, lower alkoxy or lower alkyl; 1-
- indanyl, 2-indanyl, (lower cycloalkyl)-(lower alkyl) or (Het)-lower alkyl wherein Het is as defined hereinbefore; or R³ and R⁴ together form a CH₂CH₂-W-group wherein W is as defined hereinbefore; and R⁵ is (1-8C)alkyl, lower cyclohexyl, 1-pyrrolidinyl-

ethyl, phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted on the aromatic portion thereof with halo, hydroxy, lower alkoxy or lower alkyl; 1indanyl, 2-indanyl, (lower cycloalkyl)-(1-3C)alkyl, 5 (Het)-(1-3C)alkyl wherein Het is as defined hereinbefore, phenylsulfonyl, 5-(dimethylamino)-1naphthylsulfonyl, (lower alkylamino)sulfonyl, {di(lower alkyl)amino}sulfonyl, (Het)-sulfonyl wherein Het is as defined hereinbefore, lower alkanoyl, (lower cycloalkyl) - (lower alkanoyl), (1-10 methylcyclohexyl)carbonyl, (lower alkoxy)carbonyl, (phenylmethoxy)carbonyl, 2-phenoxyacetyl, 2phenoxyacetyl monosubstituted or disubstituted on the phenyl ring with a substituent selected independently from the group consisting of bromo, 15 chloro, fluoro, iodo, methoxy and methyl; phenyl-(1-3C)alkanoyl, phenyl-(1-3C)alkanoyl monosubstituted or disubstituted with a substituent selected independently from the group consisting of azido, 20 bromo, chloro, fluoro, iodo, methoxy and methyl; $(\text{Het}) - (\text{CH}_2)_n C(0)$ wherein Het and n are as defined hereinbefore, $(Het)-Y-(CH_2)_nC(O)$ wherein, Het, Y and n are as defined hereinbefore, 2-{(lower alkoxycarbonyl)amino}-1-oxoethyl, (lower alkylamino)carbonyl, {di(lower alkyl)amino}carbonyl or (lower 25 alkylamino)thiocarbonyl; or a therapeutically acceptable acid addition salt thereof.

A more preferred set of Group 1 compounds is represented by Group 1-formula 1 wherein R¹ is hydrogen, amino, methyl, methylamino, dimethylamino, acetylamino, (1,1-dimethylethoxycarbonyl)amino or {(1,1-dimethylethylamino)carbonyl}amino; R² is hydrogen or methyl; Q is absent or methylene; R³ is

hydrogen, methyl or phenylmethyl; R4 is hydrogen, methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2dimethylpropyl, 1-propylbutyl, 2-(dimethylamino)ethyl, phenylmethyl, 1(R)-phenylethyl, 1(S)phenylethyl, 2-phenylethyl, (4-chlorophenyl) methyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4fluorophenyl)methyl, (4-methoxyphenyl)methyl, (2methylphenyl)methyl, 1-indanyl, 2-indanyl, cyclopentylmethyl, cyclohexylmethyl, 1(S)-cyclohexyl-10 ethyl, 2-cyclohexylethyl, 2-(4-morpholinyl)ethyl, 2pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl or 3thienylmethyl; and R⁵ is methyl, ethyl, propyl, 15 butyl, 2,2-dimethylpropyl, 1-propylbutyl, cyclohexyl, 1-pyrrolidinylethyl, phenylmethyl, 1(R)phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, (4chlorophenyl) methyl, (2-fluorophenyl) methyl, (3fluorophenyl)methyl, (4-fluorophenyl)methyl, (2-20 hydroxyphenyl)methyl, 4-(methoxyphenyl)methyl, (2methylphenyl)methyl, 1-indanyl, 2-indanyl, cyclopentylmethyl, cyclohexyl-methyl, 2cyclohexylethyl, 2-(4-morpholinyl)ethyl, 2pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinyl-25 methyl, 2-thienylmethyl, phenylsulfonyl, 5-(dimethylamino)-1-naphthylsulfonyl, (dimethylamino)sulfonyl, 4-morpholinylsulfonyl, acetyl, 2-methylpropionyl, 2,2-dimethylpropionyl, 3,3-dimethylbutyryl, cyclopentylcarbonyl, cyclohexylcarbonyl, 30 cycloheptylcarbonyl, cyclopentylacetyl, cyclohexylacetyl, cycloheptylacetyl, (1-methylcyclohexyl)carbonyl, (1-methylethoxy)carbonyl, (1,1dimethylethoxy)carbonyl, (2-methylpropoxy)carbonyl, (phenylmethoxy)carbonyl, (2-phenoxy)acetyl, 2-(4,6-

- 31 -

dimethylphenoxy)acetyl, benzoyl, phenylacetyl, (4azidophenyl)carbonyl, (2-fluorophenyl)carbonyl, (3fluorophenyl) carbonyl, (4-fluorophenyl) carbonyl, (2,6-dimethylphenyl)carbonyl, 4-(1-methylpiperidinyl)carbonyl, 2-(4-imidazolyl)acetyl, 2-pyridinyl-5 carbonyl, 3-pyridinylcarbonyl, 4-pyridinylcarbonyl, N-oxido-4-pyridinylcarbonyl, 2-pyridinylacetyl, 4pyridinylacetyl, 6-(2,4-dihydroxypyrimidinyl)carbonyl, 2-pyrazinylcarbonyl, 2-thienylcarbonyl, 3-10 thienylcarbonyl, 4-morpholinylcarbonyl, 4piperidinylcarbonyl, 2-(2-pyrimidinylthio)acetyl, 2-dimethylethoxy)piperidinyl}carbonyl, 2-{(1,1dimethylethoxycarbonyl)amino}-1-oxoethyl, (1,1dimethylethylamino)carbonyl, (N, N-dibutylamino)-15 carbonyl, {N-methyl-N-(1,1-dimethylethyl)amino}carbonyl, or (1,1-dimethylethylamino)thiocarbonyl; or ${\rm R}^3$ and ${\rm R}^4$ together form a ${\rm CH_2CH_2CH_2}$ group and ${\rm R}^5$ is butyl, 2,2-dimethylpropyl, 1-propylbutyl, benzyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, 20 acetyl, 2-methylpropionyl, 2,2-dimethylpropionyl, 3,3-dimethylbutyryl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, cyclopentylacetyl, cyclohexylacetyl, cycloheptylacetyl, (1methylcyclohexyl)carbonyl, (1-methylethoxy)carbonyl, 25 (1,1-dimethylethoxy)carbonyl, (2-methylpropoxy)carbonyl or benzoyl, or \mathbb{R}^3 and \mathbb{R}^4 together form a CH₂CH₂C(O) group (wherein C(O) is linked to the adjoining nitrogen atom), and R⁵ is butyl, 30 phenylmethyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 2phenylethyl, cyclopentylmethyl, cyclohexylmethyl or 2-cyclohexylethyl; or a therapeutically acceptable acid addition salt thereof.

A most preferred set of Group 1 compounds is represented by Group 1-formula 1 wherein R1 is hydrogen, amino, methylamino or dimethylamino; R2 is hydrogen or methyl; Q is absent; R3 is hydrogen, methyl or phenylmethyl; R4 is methyl, phenylmethyl, 5 1(R)-phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, (4-chlorophenyl) methyl, (2-fluorophenyl) methyl, (4fluorophenyl)methyl, (4-methoxyphenyl)methyl, (2methylphenyl) methyl, 2-pyridinylmethyl, 3pyridinylmethyl, 4-pyridinyl-methyl, 2-(2-10 pyridinyl) ethyl or 2-thienylmethyl; and R5 is 2,2dimethylpropionyl, 3,3-dimethylbutyryl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, cyclopentylacetyl, cyclohexylacetyl, (1-methylcyclohexyl)carbonyl, (1,1-dimethylethoxy)-15 carbonyl, (2-methylpropoxy)carbonyl, benzoyl, (4fluorophenyl) carbonyl, (2,6-dimethylphenyl) carbonyl, 2-pyridinylcarbonyl, 3-pyridinylcarbonyl, 4pyridinylcarbonyl, 4-morpholinylcarbonyl or (1,1-20 dimethylethylamino)carbonyl; and the carbon atom bearing the R3 group when R3 is methyl or phenylmethyl has the (R) or (S) configuration; or R^3 and R4 together form a CH₂CH₂CH₂ group and R⁵ is cyclohexylcarbonyl, and the carbon atom bearing R3 25 (i.e the carbon atom linked to the CH₂CH₂CH₂ group) has the (S) or (R) configuration; or a therapeutically acceptable acid addition salt thereof.

Still another set of most preferred Group 1

compounds is represented by Group 1-formula 1

wherein R¹ is amino, methylamino, dimethylamino,

acetylamino, (1,1-dimethylethoxy)carbonylamino or

((1,1-dimethylethylamino)carbonyl)amino; R² is

hydrogen; Q is absent or methylene; R³ is hydrogen

- 33 -

or phenylmethyl; R^4 is hydrogen, methyl, 2,2dimethylpropyl, phenylmethyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-methylphenyl)methyl, 1-indanyl, 2indanyl, cyclohexylmethyl, 2-pyridinylmethyl, 3-5 pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl or 2-thienylmethyl; and R⁵ is methyl, phenylmethyl, (2-fluorophenyl)methyl, (4fluorophenyl)methyl,(2-hydroxyphenyl)methyl, 4morpholinylsulfonyl, 2,2-dimethylpropionyl, 3,3-10 dimethylbutyryl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, cyclopentylacetyl, cyclohexylacetyl, (1,1dimethylethoxy)carbonyl, (2-methylpropoxy)carbonyl, (2-phenoxy) acetyl, 2-(2,6-dimethylphenoxy) acetyl, 15 benzoyl, phenylacetyl, 2-pyridinylcarbonyl, 3pyridinylcarbonyl, 4-pyridinylcarbonyl, 2pyridinylacetyl, 4-morpholinylcarbonyl, 2thienylcarbonyl, 2-thienylacetyl, {(1,1-dimethyl-20 ethyl)amino}carbonyl, {(1,1-dimethylethyl)amino}thiocarbonyl or 2-(4,6-dimethyl-2pyrimidinylthio)acetyl; and the carbon atom bearing the \mathbb{R}^3 group when \mathbb{R}^3 is phenylmethyl has the (R) or (S) configuration; or \mathbb{R}^3 and \mathbb{R}^4 together form a CH2CH2CH2 group and R5 is cyclohexylcarbonyl or 25 benzoyl, and the carbon atom linked to the $\mathrm{CH_2CH_2CH_2}$ group has the (R) or (S) configuration; or R^3 and R^4 together form a CH2CH2C(O) group (wherein C(O) is linked to the adjoining nitrogen atom), and \mathbb{R}^5 is phenylmethyl or cyclohexylmethyl, and the carbon 30 linked to the terminal methylene of the $CH_2CH_2C(O)$ group has the (R) or (S) configuration; or a therapeutically acceptable acid addition salt thereof.

Included within the scope of this invention is a pharmaceutical composition comprising an antiherpes virally effective amount of a compound of Group 1 as defined herein, or a therapeutically acceptable acid addition salt thereof, and a pharmaceutically or veterinarily acceptable carrier.

Still another aspect of this invention involves a

10 method for treating acyclovir-resistant herpes
infections in a mammal which comprises administering
to the mammal an anti-acyclovir-resistant herpes
effective amount of a compound of Group 1 as defined
herein, or a therapeutically acceptable acid
addition salt thereof.

Process for preparing compounds of Group 1

The compounds of Group 1 can be prepared by a

20 variety of processes. Description of some such
methods are found in standard textbooks such as
"Annual Reports In Organic Synthesis - 1994", P.M.
Weintraub et al., Eds., Academic Press, Inc., San
Diego, CA, USA, 1994 (and the preceding annual

reports), "Vogel's Textbook of Practical Organic Chemistry", B.S. Furniss et al., Eds., Longman Group Limited, Essex, UK, 1986, and "Comprehensive Organic Synthesis", B.M. Trost and I. Fleming, Eds., Pergamon Press, Oxford, UK, 1991, Volumes 1 to 8.

30

One general process is represented by Group 1-scheme 1:

- 35 -

Group 1 - Scheme 1

wherein R^1 , R^2 , Q, R^3 and R^5 are as defined herein and R^{4AA} is an amino protecting group or a radical as defined for R^4 hereinbefore other than hydrogen.

According to Group 1-scheme 1, a thiazolylaniline derivative of formula 2 is coupled with an amino acid derivative of formula 3 to give a corresponding aminoamide of formula 4. In the instance where R4AA 10 has the same significance as R4 but excluding hydrogen, then the aminoamide of formula 4 so obtained is a compound of Group 1-formula 1. instance where R4AA is an amino protecting group, the compound of formula 4 so obtained can be 15 deprotected to give the corresponding compound of Group 1-formula 1 in which R^4 is hydrogen. latter product, albeit a compound of Group 1-formula 1, can also serve as an intermediate for further elaboration by standard methods to yield compounds 20 of Group 1-formula 1 in which R4 is other than hydrogen.

The coupling of the 4-thiazolylaniline derivative of formula 2 and the amino acid of formula 3 is effected by the classical dehydrative coupling of a free carboxyl of one reactant with the free amino 5 group of the other reactant in the presence of coupling agent to form a linking amide bond. Description of such coupling agents are found in general textbooks on peptide chemistry; for example, M. Bodanszky, "Peptide Chemistry", 2nd rev ed, 10 Springer-Verlag, Berlin, Germany, 1993. Examples of suitable coupling agents are N, N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole in the presence of N, N'-dicyclohexylcarbodiimide or Nethyl-N'-{(3-dimethylamino)propyl}carbodiimide. A very practical and useful coupling agent is the 15 commercially available (benzotriazol-1-yloxy) tri-(dimethylamino) phosphonium hexafluorophosphate, either by itself or in the presence of 1hydroxybenzotriazole. Still another very practical 20 and useful coupling agent is commercially available 2-(1H-benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium tetrafluoroborate.

The coupling reaction is conducted in an inert solvent, e.g. dichloromethane, dimethylformamide, tetrahydrofuran or acetonitrile. An excess of a tertiary amine, e.g. diisopropylethylamine or N-methylmorpholine, is added to maintain the reaction mixture at a pH of about eight. The reaction temperature usually ranges between 0° and 50 °C and the reaction time usually ranges between 15 minutes and 24 hours.

- 37 -

A practical and convenient variation of the preceding process (Group 1-scheme 1) can be practiced by replacing the 4-thiazolylaniline derivative 2 with 4'-aminoacetophenone. This process is illustrated by Group 1-scheme 2:

Group 1- Scheme 2

Me (O) C

(5)

$$(5)$$
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (5)
 (6)
 (6)
 (6)
 (6)
 (6)
 (7)
 (8)
 (8)
 (8)
 (8)
 (8)
 (8)
 (8)
 (8)
 (8)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)
 (1)

wherein R^{2AA} is lower alkyl and R^3 , R^{4AA} , R^5 and Q are as defined hereinbefore.

In Group 1-scheme 2, the compound of formula 5, namely 4'-aminoacetophenone, is coupled with amino acid derivative of formula 3, noted hereinbefore, to give a corresponding terminal methyl ketone of formula 6.

The methyl ketone 6 can be used to prepare compounds of Group 1-formula 1 wherein R2 is hydrogen as follows: The methyl ketone was reacted with 10 thiourea and iodine according to the method of R.M. Dodson and L.C. King, J. Amer. Chem Soc. 1945, 67, 2242 to give the corresponding aminothiazole derivative of formula 7. In the instance where R4AA has the same significance as R4 but excluding hydrogen, then the aminothiazole derivative of 15 formula 7 so obtained is a compound of Group 1formula 1. In the instance where R^{4AA} is an amino protecting group then the derivative of formula 7 so obtained can be deprotected to give a corresponding 20 compound of Group-1-formula 1 wherein R4 is hydrogen. If desired, the latter derivative can be converted by standard methods (e.g., N-alkylation, acylation, carbamate formation, etc.) with the appropriate agent to give corresponding compounds of 25 formula 1 wherein R4 is as defined hereinbefore other than hydrogen.

Alternately, the methyl ketone of formula 6 can be used to prepare compounds of Group 1-formula 1

30 wherein R² is lower alkyl. Accordingly, the methyl ketone of formula 6 is subjected to N-alkylation with an appropriate lower alkyl bromide, chloride or iodide in the presence of a base to give the corresponding N-alkylated derivative of formula 8

- 39 -

wherein R^{2AA} is lower alkyl and Q, R^3 , R^{4AA} and R^5 are as defined hereinbefore. The latter compound, when R^{4AA} is a radical as defined for R^4 of the compound of formula 1 other than hydrogen, can be 5 transformed directly to the corresponding compound of Group 1-formula 1, wherein \mathbb{R}^1 is amino, \mathbb{R}^2 is lower alkyl, R4 is a radical other than hydrogen and Q, R^3 and R^5 are as defined hereinbefore. transformation is effected by employing the previously noted method of Dodson and King for 10 aminothiazole formation. On the other hand, the Nalkylated derivative of formula 8 wherein R4AA is an amino protected group can be deprotected to give the corresponding compounds of Group 1-formula 1 wherein \mathbb{R}^1 is amino, \mathbb{R}^2 is lower alkyl, \mathbb{R}^4 is hydrogen, and 15 Q, \mathbb{R}^3 and \mathbb{R}^5 are as defined hereinbefore.

Still another variation is illustrated by Group 1-scheme 3:

20

25

30

Group 1 - Scheme 3

$$(PG)-NH \longrightarrow N$$

$$S \longrightarrow (9)$$

$$(PG)-NH \xrightarrow{S} NHC(O)CH_2N-R^5$$

$$(11)$$

- 1 (\mathbb{R}^1 is \mathbb{NH}_2 , \mathbb{R}^2 and \mathbb{R}^3 each is H, Q is absent and \mathbb{R}^4 and \mathbb{R}^5 are as defined herein)
- 5 wherein PG is an amino protecting group, R^1 is amino, R^2 and R^3 each is hydrogen, Q is absent and R^4 and R^5 are as defined hereinbefore.
- According to Group 1-scheme 3, the protected

 aminothiazole derivative of formula 9 wherein PG
 represents an amino acid protecting group is reacted
 with bromoacetyl bromide to give the corresponding
 bromoacetamide 10. Displacement of the bromine of
 the latter compound with the appropriate primary or
 secondary amine gives the corresponding intermediate
 of formula 11. Removal of the protecting group PG

-41 -

from the latter intermediate gives the desired compound of Group 1-formula 1.

Still another variation, which can be used for

preparing compounds of Group 1-formula 1 in which Q
is methylene, is the process represented by Group 1scheme 4:

Group 1 - Scheme 4

10 wherein R^1 is NH_2 , R^2 and R^3 each is hydrogen, Q is methylene, R^{4BB} and R^{5BB} respectively have the same

significance as R^4 and R^5 as described herein, and PG is as amino protection group.

- According to Group 1-scheme 4, N-(4-acetylphenyl)-2propenamide is reacted with the appropriate primary or secondary amine to give the Michael adduct of formula 13 wherein R^{4BB} and R^{5BB} respectively have the same significance as defined for R4 and R5 hereinbefore. Thereafter, the Michael adduct of formula 13 wherein R4BB is other than hyrogen is 10 transformed to corresponding compounds of Group 1formula 1 by the previously noted method of Dodson and King for aminothiazole formation. However, in the instance wherein R4BB of the Michael adduct is hydrogen, the transformation to corresponding 15 compounds of Group 1-formula 1 proceeds with protecting the inherent secondary amine with an
- amino protecting group and the resulting amino protected derivative of formula 14 then is subjected to the Dodson and King method of aminothiazole formation, whereby the amino protecting group is cleaved in situ and the corresponding compound of Group 1-formula 1 wherein R⁴ is hydrogen is obtained. If desired, the compounds of Group 1-
- 25 formula 1 so obtained according to Group 1-scheme 4 can also serve as intermediates for elaboration to other compounds of Group 1-formula 1 in which Q is methylene by conventional methods.
- The amino acid derivative of formula 3, noted in Group 1-schemes 1 and 2, can be prepared readily by methods used in peptide chemistry. For example, the N-monosubstituted and N,N-disubstituted glycine derivatives of formula 3, wherein Q is absent, can

- 43 -

be prepared by substituting the bromine of the appropriate ethyl bromoacetate with an appropriate primary or secondary amine in the presence of a tertiary amine for example, triethylamine or Nmethylmorpholine, to obtain the corresponding α aminoester having either a monosubstituted or disubstituted amino group. Subsequent hydrolysis with lithium hydroxide of the latter product (or an amino protected derivative thereof in the process involving the primary amine), gives the desired protected N-monosubstituted, or the desired N, Ndisubstituted amino acid derivative of formula 3 wherein Q is absent. Likewise, N, N-disubstituted β amino acids of formula 3, wherein Q is methylene, can be prepared by a similar process wherein the ethyl bromoacetate derivative is replaced with the appropriate 3-bromopropionic ethyl ester derivative.

Examples of amino protective groups suitable for use in the above schemes include benzyloxycarbonyl, tert-butoxycarbonyl, 4-methoxybenzyloxycarbonyl or 2,2,2-trichloroethoxycarbonyl.

Other starting materials for the preceding processes are known or they can readily be prepared by standard methods from known starting materials. For example, 4'-aminoacetophenone (5) is available from the Aldrich Chemical Co., Milwaukee, WI, USA; and the requisite thiazolylaniline derivatives of formula 2 can be obtained by applying the classical thiazole preparation involving reacting the appropriate thioamide or thiourea of formula $H_2N-C(S)-R^1$ wherein R^1 is hydrogen, amino, lower alkylamino or di(lower alkyl)amino with 2-bromo-4'-

5

10

15

25

30

nitroacetophenone (Aldrich Chemical Co.) according to method described by R.H. Wiley et al., Organic Reactions 1951, 6, 369-373 followed by reducing the intermediate product (with a nitro group) with iron powder in the presence of hydrochloric acid to obtain the desired thiazolylaniline derivative of formula 2 wherein R¹ is as defined in the last instance. Moreover, the preparation of N-(4-acetylphenyl)-2-propenamide (12) of Group 1-scheme 4 is described in example 8 herein; and the preparation of an example of the versatile starting material of formula 9 of Group 1-scheme 3 (wherein PG is tert-butoxycarbonyl) is given in example 1 herein.

15

20

25

10

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, the reaction can be successfully performed by conventional modification known to those skilled in the art, e.g. by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, or by modification illustrated in the examples herein.

30

Furthermore, if desired, the compound of Group 1formula 1 can be obtained in the form of a
therapeutically acceptable acid addition salt. Such
salts can be considered as biological equivalent of

- 45 -

the compounds of Group 1-formula 1. Examples of such salts are those formed with hydrochloric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid or citric acid.

5

20

Antiherpes Activity

The antiviral activity of the compounds of Group 1formula 1 can be demonstrated by biochemical,

microbiological and biological procedures showing
the inhibitory effect of the compounds on the
replication of herpes simplex viruses, types 1 and 2
(HSV-1 and HSV-2), cytomegalovirus, as well as
acyclovir-resistant herpes simplex viruses and
ganciclovir-resistant cytomegaloviruses.

A biochemical procedure for demonstrating antiherpes activity for compounds of Group 1-formula 1 is described in the Group 1 examples hereinafter (see, for instance, Group 1, example 16). This particular assay is based on the evaluation of the ability of the test compound to inhibit HSV-1 helicase-primase, an essential enzyme for viral DNA replication.

- 25 Methods for demonstrating the inhibitory effect of the compounds of Group 1-formula 1 on herpes viral replication involving in vitro and cell culture techniques are desribed in example 16 herein.
- The therapeutic effect of the compounds of Group 1formula 1 can be demonstrated in laboratory animals,
 for instance, the hairless mouse model for the
 topical treatment of cutaneous HSV-1 infections,
 P.H. Lee et al., International Journal of

Pharmaceutics, 1993, 93, 139; the (HSV-2)-induced genitalis mouse model, R.W. Sidewell et al., Chemotherapy, 1990, 36, 58; and BALB/C mouse model infected with murine cytomegalovirus, D.L. Barnard et al., Antiviral Res., 1993, 22, 77, and J. Neyts et al., Journal of Medical Virology, 1992, 37, 67.

When a compound of Group 1-formula 1, or one of its therapeutically acceptable acid addition salts, is 10 employed as an antiviral agent, it is administered orally, topically or systemically to warm-blooded animals, e.g. humans, pigs or horses, in a vehicle comprising one or more pharmaceutically acceptable carriers, the proportion of which is determined by 15 the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For oral administration, the compound or a therapeutically acceptable salt thereof can be formulated in unit dosage forms such 20 as capsules or tablets each containing a predetermined amount of the active ingredient. ranging from about 25 to 500 mg, in a pharmaceutically acceptable carrier. For topical administration, the compound can be formulated in 25 pharmaceutically accepted vehicles containing 0.1 to 5 percent, preferably 0.5 to 5 percent, of the active agent. Such formulations can be in the form of a solution, cream or lotion.

For parenteral administration, the compound of Group 1-formula 1 is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. For administration by

- 47 -

injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic.

Suitable vehicles or carriers for the above noted formulations are described in standard

10 pharmaceutical texts, e.g. in "Remington's The Science and Pratice of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms And Drugs Delivery Systems", 6th ed., H.C. Ansel et al., Eds., Williams & Wilkins, Baltimore, Maryland, 1995.

The dosage of the compound will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the 20 particular host under treatment. Generally, treatment is initiated with small increments until the optimum effect under the circumstance is reached. In general, the compound of Group 1-formula 1 is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

For oral administration, the compound or a

therapeutically acceptable salt is administered in
the range of 10 to 200 mg per kilogram of body
weight per day, with a preferred range of 25 to 150
mg per kilogram.

With reference to topical application, the compound of Group 1-formula 1 is administered topically in a suitable formulation to the infected area of the body e.g. the skin, the eye, the genitalia or part of the oral cavity, in an amount sufficient to cover the infected area. The treatment should be repeated, for example, every four to six hours until lesions heal.

10 For ocular administration, the compound of Group 1formula 1 is administered either topically or
intraocularly (injection or implant) in a suitable
preparation. For example, an implant containing the
compound in a suitable formulation can be surgically
15 placed in the posterior segment of the eye through a
small incision.

With reference to systemic administration, the compound of Group 1-formula 1 is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the aforementioned variations will occur. However, a dosage level that is in the range of from about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

Although the formulations disclosed hereinabove are indicated to be effective and relatively safe medications for treating herpes viral infections, the possible concurrent administration of these formulations with other antiviral medications or agents to obtain beneficial results also included. Such other antiviral medications or agents include the antiviral nucleosides, for example, acyclovir,

- 49 -

penciclovir, famciclovir, valacyclovir and ganciclovir, and antiviral surface active agents or antiviral interferons such as those disclosed by S.S. Asculai and F. Rapp in U.S. patent 4,507,281, March 26, 1985.

The following examples (Group 1 examples) further illustrate this invention. Temperatures are given in degrees Celsius. Solution percentages or ratios express a volume to volume relationship, unless 10 stated otherwise. Nuclear magnetic resonance spectra were recorded on a Bruker 400 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. The concentrations for the 15 optical rotations are expressed in grams of the compound per 100 mL of solution. Abbreviations or symbols used in the Group 1 examples include ATP: adenosine triphosphate; Boc: tert-butoxycarbonyl or 1,1-dimethylethoxycarbonyl; BOP: (benzotriazole-1yloxy)tris-(dimethylamino)phosphonium hexafluoro-20 phosphate; Bu: butyl; DIPEA: diisopropylethylamine; DMAP: 4-(dimethylamino)pyridine; DMF: dimethylformamide; DMSO: dimethylsulphoxide; Et: ethyl; EtOAc: ethyl acetate; Et₂O: diethyl ether; Et₃N: 25 triethylamine; MS (FAB) or FAB/MS: fast atom bombardment mass spectrometry; Hex: hexane; mAb: monoclonal antibody; Me: methyl; MeOH: methanol; PFU: plaque forming units; Ph: phenyl; Pr: propyl; TBTU: 2-(1H-benzotriazol-1-yl)-N,N,N',N'-30 tetramethyluronium tetrafluoroborate; TFA: trifluoroacetic acid; THF: tetrahydrofuran.

5

GROUP 1 EXAMPLES

Example 1

- 5 tert-Butyl N-{4-(4-Aminophenyl)-2-thiazolyl}carbamate
- a) 2,2,2-Trichloroethyl N-{4-(2-amino-4-thiazolyl)phenyl)carbamate: 2,2,2-Trichloroethyl chloroformate 10 (72.3 mL, 0.52 mol) was added (5 min) to an ice cold suspension of 4'-aminoacetophenone (67.6 g, 0.50 mol) and pyridine (50.5 mL, 0.62 mol). The reaction mixture was stirred at 0° for 15 min and then at room temperature (20-22°) for 45 min. The solvent was removed under reduced pressure. Et₂O (500 mL) and 1N aqueous HCl (500 mL) were added to the residue. The resulting solid was collected by filtration, washed with H_2O (1 L) and Et_2O (1 L), and dried over P2O5 in a desiccator under reduced 20 pressure for 15 h to yield the expected carbamate (137.8 g, 89% yield). A mixture of the crude carbamate (137.8 g, 0.44 mol), thiourea (135.0 g, 1.77 mol) and I_2 (202.6 g, 0.80 mol) in isopropanol (670 mL) was heated at reflux for 18 h. reaction mixture was cooled to room temperature and 25 EtOAc (1 L) was added. The solution was successively washed with H_2O (2 x 600 mL), saturated aqueous NaHCO₃ (2 x 1 L) and then H_2O (2 x 1 L). A mixture of the organic layer and saturated aqueous 30 4N HCl (750 mL) was stirred vigorously at room temperature for 1.5 h. Et₂O (-800 mL) and H₂O (-300mL) were added to the mixture to facilitate stirring. The suspension was filtered and the solid

- 51 -

was washed with a 1:1 mixture of EtOAc and Et₂O (2

SUBSTITUTE SHEET (RULE 26)

L). The solid was suspended in 20% aqueous NaOH (1.2 L). The mixture was extracted with EtOAc. The EtOAc extract was washed with brine (700 mL), dried (MgSO₄) and concentrated under reduced pressure to yield 2,2,2-trichloroethyl N-{4-(2-amino-4-thiazolyl)phenyl}carbamate (117.7 g, 75% yield) as a pale yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ 10.18 (s, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.01 (s, 2H) 6.88 (s, 1H), 4.95 (s, 2H); MS (FAB) m/z 366/368/370/372 (MH)+.

b) The title compound: A solution of (Boc)₂O (87.7 g, 0.40 mol) in CH_2Cl_2 and DMAP(4.08 g, 33.0 mmol)was added (10 min) to a cooled (0°) solution of the 15 product of preceding section a) (117.7g, 0.33 mol) and pyridine (135.0 mL, 1.67 mol) in THF (500 mL) and CH₂Cl₂ (1 L). The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with EtOAc (1.5 L) and Et₂O (1 L). 20 resulting solution was washed serially with H_2O (1 L), 10% (w/v) aqueous citric acid (2 x 500 mL), 1N aqueous HCl (500 mL), H2O, saturated aqueous NaHCO3 $(2 \times 1 L)$ and brine (1 L), dried $(MgSO_4)$ and concentrated under reduced pressure to give a pale 25 yellow foam (163 g). The latter foam (160 g, 0.34 mol) was diluted in 1,4-dioxane (1.72 L). solution cooled to 10°. Zn powder (224 g, 3.43 mol) and 1N aqueous HCl (3.4 L) were added to the cooled solution. The reaction mixture was mechanically 30 stirred at room temperature for 1.5 h. suspension was filtered. The collected material was washed with 1N aqueous HCl (-1 L). Aqueous 20% NaOH (2 L) was added to the filtrate (including the acidic wash). The resulting mixture was extracted

with EtOAc (9 L total). The EtOAc extract was
filtered through diatomaceous earth. The filtrate
was washed with brine, dried (MgSO₄) and
concentrated under reduced pressure. Purification
by flash chromatography (SiO₂, EtOAc: Hex, 1:2 to
2:3) of the residue gave the title compound (48.3 g,
49% yield) as a pale yellow foam: ¹H NMR (400 MHz,
DMSO-d₆) δ 11.40 (s, 1H), 7.52 (d, J=7.2 Hz, 2H),
7.12 (s, 1H), 6.57 (d, J=7.2 Hz, 2H), 5.20 (s, 2H),
10 1.48 (s, 9H); MS (FAB) m/z 292 (MH) +.

Example 2

- N- $\{4-(2-Amino-4-thiazolyl) phenyl\}-2-\{(phenylmethyl)-amino\}$ acetamide (1: R¹, R², R³ and R⁴=H, R⁵=CH₂Ph and Q=valance bond)
- tert-Butyl N-(2-hydroxy-2-oxoethyl)-N-20 (phenylmethyl)carbamate: To a cold (-20°) suspension of 60% NaH (120 g, 3.00 mol) in THF (700 mL) was added (30 min) a solution of Boc-glycine (175 g, 1.00 mol) in THF (300 mL). Thereafter, benzyl bromide was added to the mixture. After 15 25 min, the cooling bath was removed. The reaction mixture was stirred at room temperature for 1 h and then heated at reflux for 16 h. The reaction mixture was cooled to 0° . H_2O (~50 mL) was added dropwise over a 30 min period. After another 30 30 min, H_2O (600 mL) was added. The mixture was washed with hexane (3 x 500 mL). 1N Aqueous HCl (1.3 L) was added slowly to the aqueous layer, followed by the addition of 4N aqueous HCl (300 mL). aqueous solution was extracted with EtOAc (1.5 L)

- 53 -

and then CH₂Cl₂ (3 x 500 mL). The combined organic
layers were serially washed with H₂O and brine,
dried (MgSO₄, Na₂SO₄, charcoal), filtered through
diatomaceous earth and concentrated under reduced

5 pressure to give the title compound (241 g, 91%
yield) as a pale yellow solid: Mp 94-97°; ¹H NMR
(400 MHz, DMSO-d₆) δ 10.5 (broad s, 1H), 7.23-7.33
(m, 5H), 4.40 (s, 2H), 3.80, 3.72 (2s, 2H), 1.38,
1.35 (2s, 9H); MS (FAB) m/z 266 (MH)⁺; Anal. Calcd
10 for C₁₄H₁₉NO₄ (and accounting for water content,
0.58% w/w as determined by Karl Fisher analysis): C,
63.01; H, 7.26; N, 5.25. Found: C, 62.79; H, 7.14;

N, 5.13.

tert-Butyl N-{2-{(4-acetylphenyl)amino}-2-15 oxoethyl}-N-(phenylmethyl)carbamate: Isobutyl chloroformate (35.1 g, 0.26 mol) was added (15 min) to an ice-cold solution of tert-butyl N-(2-hydroxy-2-oxoethyl)-N-(phenylmethyl)carbamate (65.0 g, 0.24 mol), described in preceding section a), and Et_3N 20 (31.0 g, 0.31 mol) in CH_2Cl_2 (610 mL). The mixture was stirred at 0° for 45 min. Solid 4'aminoacetophenone (34.8 g, 0.26 mol) was added portion wise to the reaction mixture. The reaction mixture was stirred at 0° for 1.5 h and then at room 25 temperature for 16 h. H_2O (10 mL) was added. resulting solution was concentrated under reduced pressure. The residue was dissolved in EtOAc (1 L). The solution was washed successively with 1N aqueous 30 HC1 (2 x 300 mL), a saturated aqueous solution of $NaHCO_3$ (2 x 300 mL) and brine (200 mL), dried $(MgSO_4)$ and concentrated under reduced pressure. The resulting brownish solid was crystallized

(EtOAc: Hex) to give the title compound (56.8 g, 61%

5

yield) as a white solid: 1 H NMR (400 MHz, CDCl₃) δ 9.72 (broad s, 1H), 7.90 (d, J=8.6 Hz, 2H), 7.40-7.54 (m, 2H), 7.26-7.39 (m, 5H), 4.55 (s, 2H), 3.96 (s, 2H), 2.56 (s, 3H), 1.51 (s, 9H); MS (FAB) m/z 383 (MH)⁺.

- The title compound: A mixture of tert-butyl N-{2-{(4-acetylphenyl)amino}-2-oxoethyl}-N-(phenylmethyl)carbamate (50.0g, 0.13 mol), described 10 in preceding section b), thiourea (39.8 g, 0.52 mol) and I_2 (66.4 g, 0.26 mol) in isopropanol (520 mL) was heated at reflux for 2.5 h. EtOAc (50 mL) was added to the cooled mixture. The resulting solid was collected by filtration. The filtrate was 15 concentrated under reduced pressure. EtOAc (500 mL) was added to the concentrate and another portion of solid was obtained by filtration. The combined solid portions were suspended in 5% aqueous Na₂CO₃. The mixture was stirred vigorously. EtOAc (2 L) was added and the two immiscible phases were separated. 20 The aqueous phase was extracted with EtOAc (2 \times 800 mL). The combined organic phases were washed with brine, dried (MgSO₄) and concentrated under reduced pressure. Purification by flash chromatography 25 (SiO2. CHCl3:EtOH, 10:1) gave the title compound (26.3 g, 59% yield) as a pale yellow solid: M.p. 162-163°; ¹H NMR (400 MHz, DMSO- d_6) δ 9.83 (s, 1H), 7.72 (d, J=8.7 Hz, 2H), 7.61 (d, J=8.7 Hz, 2H), 7.31-7.38 (m, 4H), 7.24 (t, J=7.2 Hz, 1H), 7.00 (s, 2H), 6.88 (s, 1H), 3.75 (s, 2H), 3.28 (s, 2H); MS 30 (FAB) m/z 339 (MH)⁺; Anal. Calcd for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.55. Found: C, 63.59; H, 5.32; N, 16.48.
 - 55 -

Example 3

N-{4-(2-Amino-4-thiazolyl)phenyl}-2-{(cyclohexylmethyl)amino)acetamide (1: R¹, R² R³ and R⁴=H,

R⁵=cyclohexylmethyl and Q=valance bond)

Method A:

- a) tert-Butyl N-(cyclohexylmethyl)-N-(2-hydroxy-210 oxoethyl)carbamate: Ethyl 2-bromoacetate (1.67 g,
 10.0 mmol) was added (5 min) to a solution of
 cyclohexanemethylamine (1.13 g, 10.0 mmol) and Et₃N
 (2.78 mL, 20.0 mmol) in THF (20 mL) at 0°. The
 mixture was stirred at 0° for 30 min, allowed to
- warm to room temperature, stirred at room temperature for 1 h and then cooled to 0°. A solution of (Boc)₂O (2.20 g, 10.1 mmol) in THF (~5 mL) was added (10 min) to the reaction mixture. The solution was stirred at 0° for 30 min and then at
- 20 room temperature for 1.5 h. A solution of LiOH. $\rm H_2O$ (1.68g, 40.0 mmol) in $\rm H_2O$ (20 mL) and MeOH (10 mL) was added to the reaction mixture. The mixture was stirred at room temperature for 2.5 h. Thereafter, the organic solvents were removed from the reaction
- 25 mixture under reduced pressure. The residual aqueous solution was diluted with $\rm H_2O$ (125 mL) and washed with a 1:1 mixture of $\rm Et_2O:Hex$ (4 x 100 mL). The aqueous layer was rendered acidic with solid citric acid (pH=3) and then extracted with EtOAc (3
- 30 x 100 mL). The EtOAc extract was washed with brine (2 x 50 mL), dried (MgSO $_4$) and concentrated under reduced pressure to give the title compound (2.09 g, 77% yield) as a white solid, which was used without further purification: ¹H NMR (400 mHz, CDCl $_3$) δ

- 3.96, 3.90 (2 broad s, 2H), 3.11 (broad s, 2H), 1.66-1.70 (m, 5H), 1.47, 1.43 (2s, 9H), 1.13-1.25 (m, 4H), 0.91 (broad s, 2H); MS (FAB) m/z 272 (MH)⁺.
- b) tert-Butyl N-{2-{(4-acetylphenyl)amino}-2-oxoethyl}-N-(cyclohexylmethyl)carbamate: To a solution of the product of preceding section a) (1.43 g, 5.30 mmol) and 4'-aminoacetophenone (712 mg, 5.30 mmol) in acetonitrile (10.6 mL) was added
- 10 TBTU (1.69 g, 5.30 mmol) and DIPEA (1.85 mL, 10.6 mmol). The reaction mixture was stirred at room temperature for 18 h. The mixture was diluted with EtOAc (200 mL). The resulting solution was washed with $\rm H_{2}O$ (50 mL), saturated aqueous NaHCO₃ (50 mL),
- brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification by flash chromatography (SiO₂, EtOAc:Hex, 1:1) of the residue gave the desired tert-butyl N-{2-{(4-acetylphenyl)amino}-2-oxoethyl}-N-(cyclohexyl-
- 20 methyl)carbamate (0.72 g, 35% yield) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 9.19 (broad s, 1H), 7.93 (d, J=8.6 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 7.26 (s, 1H), 3.97 (s, 2H), 3.19 (d, J=7.0 Hz, 2H), 2.57 (s, 3H), 1.61-1.69 (m, 5H), 1.50 (s, 9H), 1.16-1.22
- 25 (m, 4H), 0.93 (broad s, 2H).
- c) The title compound: A mixture of the product of preceding section b) (720 mg, 1.85 mmol), thiourea (282 mg, 3.71 mmol) and I_2 (704 mg, 2.78 mmol) in isopropanol (10 mL) was heated at reflux for 15 h. The reaction mixture was poured into H_2O (125 mL) and the resulting mixture was washed with Et_2O (4 x 100 mL). The aqueous layer was rendered

- 57 -

basic by addition of saturated aqueous $NaHCO_3$ and then extracted with EtOAc (2 \times 100 mL). The combined EtOAc extracts were dried (MgSO4) and concentrated under reduced pressure. The residue 5 was purified by flash chromatography (SiO2, CH2Cl2: MeOH, 15:1) to give the title compound of this example (355 mg, 56% yield) as a light yellow solid: M.p. 164-166°; ¹H NMR (400 MHz, DMSO-d₆) δ 9.79 (broad s, 1H), 7.72 (d, J=8.7 Hz, 2H), 7.60 (d, J=8.7 Hz, 2H), 7.00 (s, 2H), 6.88 (s, 1H), 3.25 (s, 10 2H), 2.37 (d, J=6.6 Hz, 2H), 1.61-1.78 (m, 5H), 1.35-1.45 (m, 1H), 1.11-1.25 (m, 3H), 0.85-0.94 (m, 2H); MS (FAB) m/z 345 (MH)+; Anal. Calcd for C₁₈H₂₄N₄OS: C, 62.76; H, 7.02: N, 16.26. Found: C, 15 62.63; H, 7.10; N, 16.26.

Method B

a) tert-Butyl N-{4-{4-{(2-bromo-1-oxoethyl)amino}-20 phenyl}-2-thiazolyl}carbamate: To an ice-cold solution of 2-bromoacetyl bromide (10.1 g, 50.0 mmol), in CH_2Cl_2 (200 mL) was added (30 min) a solution of tert-butyl $N-\{4-(4-aminophenyl)-2$ thiazolyl)carbamate (14.6 g, 50.0 mmol, described in 25 example 1) and pyridine (4.04 mL, 50.0 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at 0° for 30 min and then at room temperature for 30 min. The reaction mixture then was diluted with in EtOAc (1.5 L). The resulting mixture was washed successively with H_2O (500 mL), 10% (w/v) aqueous 30 citric acid (2 x 500 mL), brine (500 mL), saturated aqueous $NaHCO_3$ (500 mL) and brine (500 mL), then dried (MgSO₄) and filtered. The organic solution was concentrated under reduced pressure to a volume

of 500 mL. The resulting suspension was filtered and the collected solid was washed with EtOAc (2 x 10 mL) to yield 13.1 g of the title compound. An additional 2.4 g was obtained by concentration of the filtrate to a volume of 25 mL giving a total of 15.5 g (75% yield) of the tert-butyl N-{4-{4-{(2-bromo-1-oxoethyl)amino}phenyl}-2-thiazolyl}carbamate as a white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 11.54 (s, 1H), 10.44 (s, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.46 (s, 1H), 4.04 (s, 2H), 1.49 (s, 9H); MS (FAB) m/z 412/414 (MH)+.

b) tert-Butyl N-{4-{4-{(cyclohexylmethyl)amino}-1-oxoethyl}amino}phenyl}-2-thiazolyl}carbamate: 15 an ice-cold solution of the product of preceding section a) (2.48 g, 6.00 mmol) in THF (60 mL) were added cyclohexanemethylamine (781 µL, 6.00 mmol) followed by Et₃N (1.67 mL, 12.0 mmol). The reaction mixture was stirred at room temperature for 4 h. H₂O (10 mL) and saturated aqueous NaHCO₃ (10 mL) 20 were added to the mixture. The solvent was removed under reduced pressure. EtOAc (200 mL), H2O (30 mL), and saturated aqueous NaHCO3 (30 mL) were added to the residual aqueous solution. The phases were separated. The organic phase was washed with H2O. 25 The solid in the suspension in the organic phase was collected on a filter. The solid was washed with H_2O (10 mL) and EtOAc (10 mL) to give a first crop of product (2.55 g). The filtrate was concentrated 30 to 25 mL and the resulting suspension filtered to afford a second crop of 0.60 g of product. manner, a total of 3.15 g (81% yield) of the title compound of this section b) was collected as a white solid: ¹H NMR (400 MHz, DMSO- d_6) δ 9.82 (broad s,

- 59 -

1H), 7.79 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.44 (s, 1H), 3.25 (s, 2H), 2.37 (d, J = 6.6 Hz, 2H), 1.59-1.78 (m, 5H), 1.35-1.44 (m, 1H), 1.14-1.27 (m, 3H), 0.85-0.94 (m, 2H).

5

10

15

25

c) The title compound of this example: A solution of the product of preceding section b) (2.40 g, 5.40 mmol) and TFA (40 mL) in $\mathrm{CH_2Cl_2}$ (40 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (250 mL), the resulting solution was washed with saturated aqueous $\mathrm{NaHCO_3}$ and brine, dried (MgSO₄) and concentrated under reduced pressure to give the title compound of this example (1.60 g, 86% yield) as a white solid. This material was found to be identical to the

20 Example 4

 $N-\{2-\{\{4-(2-Amino-4-thiazolyl)phenyl\}amino\}-2-oxoethyl\}-N-(phenylmethyl)cyclohexanecarboxamide (1: R¹, R² and R³=H, R⁴=PhCH₂, R⁵=cyclohexylcarbonyl and Q=valance bond)$

product prepared by method A of this example.

To a solution of N-{4-(2-amino-4-thiazolyl)phenyl}2-{(phenylmethyl)amino}acetamide (352 mg, 1.04 mmol,
described in example 2), cyclohexanecarboxylic acid
(140 mg, 1.09 mmol) and DIPEA (269 mg, 2.08 mmol) in
DMF (5.2 mL) was added TBTU (350 mg, 1.09 mmol).
The mixture was stirred at room temperature for 6 h.
The reaction mixture was diluted with EtOAc (125
mL). The resulting solution was washed with

saturated aqueous NaHCO3 (40 mL), H2O (40 mL), and brine (40 mL), then dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO2, CHCl3: EtOH, 15:1) to yield the title compound (341 mg, 73% yield) as a white solid: M.p. 214.5-215.5°; ¹H NMR (400 MHz, DMSO-d₆) δ (2 rotamers, 1:1) 10.06, 9.92 (2 s, 1H), 7.73, 7.71 (2 d, J = 8.5 Hz, 2H), 7.56, 7.55 (2 d, J= 8.5 Hz, 2H, 7.20-7.41 (m, 5H), 7.01, 7.00 (2 s, 5Hz)10 2H), 6.89, 6.88 (2 s, 1H), 4.70, 4.51 (2 s, 2H), 4.13, 4.02 (2 s, 2H), 2.64, 2.56 (2 broad t, J =10.5 Hz, 1H), 1.61-1.70 (m, 5H), 1.12-1.46 (m, 5H); MS (FAB) m/z 449 (MH)⁺; Anal. Calcd for $C_{25}H_{28}N_4O_2S$: C. 66.94; H, 6.29; N, 12.49. Found: C, 66.54; H, 6.29; N, 12.32. 15

Example 5

- 20 N-{2-{{4-(2-Amino-4-thiazolyl)phenyl}amino}-2-oxoethyl}-N-(1,1-dimethylethyl)-N-(phenylmethyl)-urea (1: R¹, R² and R³=H, R⁴=PhCH₂, R⁵=C(O)NHCMe₃ and Q=valance bond)
- 25 tert-Butyl isocyanate (114 mL, 1.00 mmol) was added
 dropwise to a solution of N-{4-(2-amino-4thiazolyl)phenyl}-2-{(phenylmethyl)amino}acetamide·2HCl (411 mg, 1.00 mmol, the corresponding
 free base has been described in example 2) and Et₃N
 30 (558 mL, 4.00 mmol) in THF (10 mL) and CH₂Cl₂ (10
 mL) at room temperature. The reaction mixture was
 stirred 18 h. The mixture was diluted with EtOAc
 (200 mL). The resulting solution was washed with

saturated aqueous NaHCO3 (75 mL), brine (75 mL),

- 61 -

dried (MgSO₄), and concentrated under reduced pressure. The pale yellow solid residue (450 mg) was recrystallized from EtOAc to give the title compound of this example (295 mg, 67%) as white crystals: M.p. 207-209°; ¹H NMR (400 MHz, DMSO-d₆) δ 9.89 (s, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 7.23-7.36 (m, 5H), 6.98 (s, 2H), 6.88 (s, 1H), 5.80 (s, 1H), 4.50 (s, 2H), 3.96 (s, 2H), 1.25 (s, 9H); MS (FAB) m/z 438 (MH)⁺; Anal. Calcd for C₂₃H₂₇N₅SO₂: C, 63.13; H, 6.22; N, 16.01. Found: C, 63.03; H, 6.24; N, 16.03.

Example 6

15

 $N-\{2-\{\{4-(2-Amino-4-thiazoly1)phenyl\}amino\}-2-oxoethyl\}-N-(phenylmethyl)-4-morpholinecarboxamide (1: R¹, R² and R³=H, R⁴=PhCH₂, R⁵=4-morpholinylcarbonyl and Q=valance bond)$

20

To a cooled (0°) suspension of N-{4-(2-amino-4-thiazolyl)phenyl}-2-{(phenylmethyl)amino}acetamide (1.02 g, 3.00 mmol, described in example 2) in CH₂Cl₂ (30 mL) and Et₃N (836 µL, 6.00 mmol), were added DMAP (36.6 mg, 0.30 mmol) and 4-morpholinecarbonyl chloride (350 µL, 3.00 mmol). The reaction mixture was stirred at 0° for 30 min, and then at room temperature for 18 h. The reaction mixture was then dissolved in EtOAc (300 mL). The resulting solution was washed with saturated aqueous NaHCO₃ (100 mL), brine (100 mL), then dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂,

EtOAc) to afford the title compound (925 mg, 68%

yield) as a white solid: M.p. 105° (decomp.); ¹H NMR (400 MHz, DMSO-d₆) δ 9.94 (s, 1H), 7.71 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 7.25-7.39 (m, 5H), 6.99 (s, 2H), 6.88 (s, 1H), 4.47 (s, 2H), 3.84 (s, 2H), 3.59 (t, J = 4.9 Hz, 4H), 3.19 (t, J = 4.9 Hz, 4H); MS (FAB) m/z 452 (MH)⁺; Anal. Calcd for $C_{23}H_{25}N_5SO_3$: C, 61.18; H, 5.58; N, 15.51. Found: C, 60.61; H, 5.60; N, 15.35.

10

Example 7

N-(4-(2-Amino-4-thiazolyl)phenyl}-2-{(4-morpholinylsulfonyl)(phenylmethyl)amino}acetamide

(1: R¹, R² and R³=H, R⁴=PhCH₂, R⁵=4-morpholinylsulfonyl and Q=valance bond)

4-Morpholinesulfonyl chloride (213 mg, 1.15 mmol) was added (5 min) to an ice-cold solution of N-{4-20 (2-amino-4-thiazolyl)phenyl}-2-{(phenylmethyl)amino)acetamide·2HCl (450 mg, 1.09 mmol), the corresponding free base has been described in example 2) and Et₃N (443 mg, 4.38 mmol) in CH₂Cl₂ (10.9 mL). The reaction mixture was allowed to warm 25 to room temperature and DMAP (14.0 mg, 0.11 mmol) was added. After standing for 37 h at room temperature, the mixture was dissolved in EtOAc (125 mL). The solution was washed successively with saturated aqueous NaHCO3 (50 mL) and brine (50 mL), 30 dried (MgSO₄) and concentrated under reduced pressure. Purification of the resulting residue by flash chromatography (SiO2, EtOAc) gave the title compound (200 mg, 38% yield) as a white solid: M.p. 193-194°; ¹H NMR (400 MHz, DMSO- d_6) δ 10.02 (s, 1H),

- 63 -

SUBSTITUTE SHEET (RULE 26)

7.73 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 7.30-7.41 (m, 5H), 7.01 (s, 2H), 6.89 (s, 1H), 4.59 (s, 2H), 3.91 (s, 2H), 3.58 (t, J = 4.6 Hz, 4H), 3.18 (t, J = 4.6 Hz, 4H); MS (FAB) m/z 488 (MH)+; Anal. Calcd for $C_{22}H_{25}N_5O_4S_2$: C, 54.19; H, 5.17; N, 14.36. Found: C, 53.63; H, 5.07; N, 14.34.

Example 8

10

N-{4-(2-Amino-4-thiazolyl)phenyl}-3-{(phenylmethyl)-amino}propanamide (1: R^1 , R^2 , R^3 =H and R^4 =H, R^5 =PhCH₂ and Q=CH₂)

- a) N-(4-Acetylphenyl)-2-propenamide: A solution of acryloyl chloride (29.5 mL, 363 mmol) in CH₂Cl₂ (50 mL) was added dropwise (30 min) to an ice-cold solution of 4'-aminoacetophenone (49.0 g, 363 mmol) and Et₃N (50.6 mL, 363 mmol) in CH₂Cl₂ (300 mL).
- The reaction mixture was stirred at 0° for 15 min and then was concentrated under reduced pressure. The residue was dissolved with EtOAc. The solution was washed successively with 10% aqueous HCl, saturated aqueous NaHCO3 and H2O. The organic phase
- was dried (MgSO₄) and concentrated under reduced pressure to afford the desired N-(4-acetylphenyl)-2-propenamide (52 g, 76% yield) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 8.17 (broad s, 1H), 7.93 (d, J = 8.9 Hz, 2H), 7.72 (d, J = 8.9 Hz, 2H), 6.47 (dd,
- 30 J = 1.0, 16.9 Hz, 1H), 6.33 (dd, J = 10.2, 16.9 Hz, 1H), 5.80 (dd, J = 1.0, 10.2 Hz, 1H), 2.58 (s, 3H); MS (FAB) m/z 190 (MH)+.

b) N-(4-Acetylphenyl)-3-{(phenylmethyl)amino}propanamide: A solution of the product of preceding section a) (2.00 g, 10.6 mmol) and benzylamine (1.27 mL, 11.6 mmol) in THF (50 mL) was heated at reflux 5 for 25.5 h. The cooled mixture was concentrated under reduced pressure. The residue was dissolved The EtOAc solution was washed with 10% with EtOAc. aqueous HCl. The resulting solid was collected on a filter and then combined with the aqueous acidic 10 This acidic suspension was rendered basic (pH=~12) with 10N aqueous NaOH. The mixture was extracted with EtOAc. The EtOAc extract was dried (MgSO₄) and concentrated under reduced pressure to afford N-(4-acetylphenyl)-3-{(phenylmethyl)amino}-15 propanamide (2.92 g) as a yellow oil which could be used directly in the next step or purified by flash column chromatography (SiO2, EtOAc) to afford 2.05 g (65% yield) of a pale yellow solid: 1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 11.1 Hz, 2H), 7.59 (d, J = 20 11.1 Hz, 2H), 7.26-7.40 (m, 5H), 3.88 (s, 2H), 3.05 (dd, J = 5.7, 6.7 Hz, 2H), 2.57 (s, 3H), 2.54 (dd, J)= 5.7, 6.7 Hz, 2H), 1.69 (s, 1H); MS (FAB) m/z 297 $(MH)^+$.

c) tert-Butyl N-{3-{(4-acetylphenyl)amino}-3-oxopropyl}-N-(phenylmethyl)carbamate: To a solution of the product of section b) (1.78 g, 5.99 mmol) and DIPEA (2.00 mL, 12.0 mmol) in THF (30 mL) was added (Boc)₂O (1.23 g, 6.59 mmol). The resulting solution was stirred at room temperature for 18 h and then concentrated under reduced pressure. The residue was dissolved with EtOAc. The EtAOc solution was washed successively with 10% aqueous HCl, saturated aqueous NaHCO₃ and brine. The organic phase was

- 65 -

dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO₂, EtOAc:Hex, 1:1) gave tert-butyl N-{3-{(4-acetylphenyl)amino}-3-oxopropyl}-N-(phenylmethyl)carbamate (2.33 g, 98% yield) as a white foam: 1 H NMR (400 MHz, CDCl₃) δ 9.20 (broad s, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.68 (broad d, J = 8.3 Hz, 2H), 7.22-7.35 (m, 5H), 4.47 (s, 2H), 3.62 (t, J = 6.7 Hz, 2H), 2.64 (broad s, 2H), 2.57 (s, 3H), 1.46 (s, 9H); MS (FAB) m/z 397 (MH+).

5

10

d) The title compound: A solution of the product of preceding section c) (2.17 g, 5.47 mmol), thiourea (1.67 g, 21.9 mmol) and I_2 (2.78 g, 10.9 mmol) in 15 isopropanol (11 mL) was heated at reflux for 5 h. The resulting suspension was cooled to room temperature and then filtered. The collected solid was suspended in a mixture of saturated aqueous $NaHCO_3$ (200 mL) and 10N aqueous NaOH (1 mL). 20 suspension was extracted with EtOAc. The EtAOc extract was dried $(MgSO_4)$ and concentrated under reduced pressure. The residue was purified by recrystallisation from EtOAc to afford the title compound (1.23 g, 64% yield) as a pale yellow solid: 25 M.p. 131-133°; ¹H NMR (400 MHz, DMSO-d₆) δ 10.10 (s, 1H), 7.70 (d, J=8.6 Hz, 2H), 7.56 (d, J=8.6 Hz, 2H), 7.22-7.32 (m, 5H), 6.99 (s, 2H), 6.87 (s, 1H), 3.73 (s, 2H), 2.80 (broad s, 2H), 2.39 (broad s, 2H); MS (FAB) m/z 353 (MH)+; Anal. Calcd for $C_{19}H_{20}N_4OS$: C, 30 64.75; H, 5.72; N, 15.90. Found: C, 63.95; H, 5.67; N, 15.92.

5

Example 9

tert-Butyl N-{2-{{4-{2-(Dimethylamino)-4-thiazolyl)phenyl}amino}-2-oxoethyl}-N-(phenylmethyl)carbamate (1: R¹=NMe₂, R² and R³=H, R⁴=PhCH₂, R⁵=C(0)OCMe₃ and Q=valance bond)

- a) N, N-Dimethyl-4-(4-nitrophenyl)-2-thiazolamine: A solution of 2-bromo-4-nitroacetophenone (4.42 g, 18.1 mmol), N,N,-dimethylthiourea (3.77 g, 36.2 10 mmol) in isopropanol (60 mL) was heated at reflux for 45 min. The cooled reaction mixture was diluted with EtOAc. The solution was washed with saturated aqueous NaHCO3, H2O and brine, dried (MgSO4) and 15 concentrated under reduced pressure to give N, Ndimethyl-4-(4-nitrophenyl)-2-thiazolamine (2.92 g, 65% yield) as an orange solid: 1H NMR (400 MHz, DMSO-d₆) δ 8.24 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.8 Hz, 2H), 7.56 (s, 1H), 3.11 (s, 6H); MS (FAB) 20 m/z 250 (MH) +.
- b) N,N-dimethyl-4-(4-aminophenyl)-2-thiazolamine:
 Iron powder (6.51 g, 116.7 mmol) and 1N aqueous HCl
 (2.3 mL) were added to a solution of N,N-dimethyl-4(4-nitrophenyl)-2-thiazolamine of section a) (2.91 g, 11.7 mmol) in EtOH (39 mL) at room temperature.
 The mixture was stirred and heated at reflux for 3 h. The hot reaction mixture was filtered through diatomaceous earth. The solid on the filter was
 washed with hot EtOH (200 mL). The filtrate was diluted with EtOAc and Et₂0 (1:1, 100 mL) and then concentrated to about 25% of its original volume.
 This solution was diluted with EtOAc (150 mL). The

- 67 -

mixture was washed successively with saturated aqueous $NaHCO_3$, H_2O and brine, then dried $(MgSO_4)$ and concentrated under reduced pressure to give N, N-dimethyl-4-(4-aminophenyl)-2-thiazolamine (2.24 g, 87% yield) as a light brown oil: 1H NMR (400 MHz, DMSO- d_6) δ 7.53 (d, J = 8.4 Hz, 2H), 6.74 (s, 1H), 6.56 (d, J = 8.4 Hz, 2H), 5.16 (s, 2H), 3.05 (s, 6H); MS (FAB) m/z 220 (MH) +. This product was used without further purification in the next section.

10

5

c) The title compound: DIPEA (4.21 mL, 24.2 mmol) was added to a solution of N, N-dimethyl-4-(4aminophenyl)-2-thiazolamine (1.77 g, 8.07 mmol, described in the previous section), tert-butyl N-(2-hydroxy-2-oxoethy1)-N-(phenylmethy1)carbamate 15 {2.35 g, 8.87 mmol, described in example 2, section a)} and BOP (3.92 g, 8.87 mmol) in DMF (8 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h then diluted with EtOAc 20 (300 mL). The solution was washed successively with H_2O (2 x 60 mL), saturated aqueous NaHCO₃ (60 mL) and brine (60 mL), dried (MgSO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography (SiO_2 , Hex:EtOAc:EtOH, 5:2:1) gave the title compound (3.13 25 g, 83% yield) as a beige solid: 1H NMR (400 MHz, DMSO- d_6) δ 9.98, 9.92 (2s, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.26-7.38 (m, 5H), 7.06 (s, 1H), 4.48 (s, 2H), 3.97, 3.86 (2s, 2H), 3.08 (s, 6H), 1.37 (s, 9H); MS (FAB) m/z 467 (MH)+; 30 Anal. Calcd for $C_{25}H_{30}N_4O_3S$: C, 64.35; H, 6.48; N, 12.01. Found: C, 64.54; H, 6.56; N, 12.12.

5

Ç

Example 10

 $N-\{4-(2-Amino-4-thiazolyl) phenyl\}-N-methyl-2-$ {(phenylmethyl)amino}acetamide (1: $R^1 = NH_2$, $R^2 = CH_3$, $R^3 = H$, $R^4 = H$ and $R^5 = PhCH_2$)

- tert-Butyl N-{2-{(4-acetylphenyl)methylamino}-2oxoethyl}-N-(phenylmethyl)carbamate: A solution of tert-butyl N-{2-{(4-acetylphenyl)amino}-2-oxoethyl}-10 N-(phenylmethyl)carbamate (1.50 g, 3.92 mmol), described in section b) of example 2, in DMF (5.5 mL) was added rapidly to a suspension of NaH (94 mg, 3.92 mmol) in DMF (10 mL) at room temperature. mixture was stirred at room temperature for 30 min. 15 Methyl iodide (366 mL, 5.88 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 18 h. The mixture was diluted with H₂O (100 mL) and the resulting solution was extracted with EtOAc (200 mL). The organic layer 20 was washed with H_2O (3 x 75 mL) and brine (75 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂, Hex:EtOAc, 1:1) to give the title compound (0.80 g, 52% yield) as a colorless 25 foam: ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, J = 8.3 Hz, 2H), 7.15-7.30 (m, 7H), 4.53, 4.56 (2s, 2H), 3.59, 3.74 (2 broad s, 2H), 3.29 (s, 3H), 2.59 (s, 3H),
- 30 b) The title compound: A solution of the product of preceding section a) (0.79 g, 1.99 mmol), thiourea (0.61 g, 7.97 mmol) and I_2 (1.01 g, 3.98 mmol) in isopropanol (5 mL) was heated at reflux for 2 h. The cooled mixture was partitioned between

1.45, 1.47 (2s, 9H); MS (FAB) m/z 397 (MH)+.

- 69 -

SUBSTITUTE SHEET (RULE 26)

saturated aqueous NaHCO3 and EtOAc (200 mL). The organic layer was washed with brine (50 mL), dried (MgSO4) and concentrated under reduced pressure. Purification by flash chromatography (SiO2, CHCl3:EtOH, 8:1) yielded the title compound (358 mg, 51% yield) as a pale yellow solid: M.p. $160-2^{\circ}$; 1 H NMR (400 MHz, DMSO-d6) δ 7.80 (d, J = 8.4 Hz, 2H), 7.17-7.27 (m, 7 H), 7.06 (s, 2H), 7.05 (s, 1H), 3.61 (broad s, 2H), 3.19 (s, 3H), 3.04 (broad s, 2H), 2.33 (broad s, 1H); MS (FAB) m/z 353 (MH)+; Anal. Calcd for $C_{19}H_{20}N_{4}OS$: C, 64.75; H, 5.72; N, 15.90. Found: C, 64.46; H, 5.63; N, 15.80.

15 Example 11

20

25

30

tert-Butyl $N-\{2-\{\{4-(2-Amino-4-thiazolyl)phenyl\}-amino\}-2-oxo-1(S)-(phenylmethyl)ethyl\}carbamate (1: <math>R^1=NH_2$, $R^2=H$, $R^3=PhCH_2$, $R^4=H$ and $R^5=Boc$, and the carbon atom bearing R^3 has the (S) configuration)

TBTU (1.61 g, 5.00 mmol) was added to a solution of 4-(4-aminophenyl)-2-thiazolamine (956 mg, 5.00 mmol), (L)-Boc-phenylalanine (1.33 g, 5.00 mmol) and DIPEA (1.74 mL, 10.0 mmol) in DMF (50 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc (250 mL). The resulting solution was washed with saturated aqueous NaHCO₃ (2 x 150 mL) and brine (100 mL), then dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂, EtOAc:Hex, 1:1) to give the title compound (1.11 g,

51% yield) as a pale brown solid. Colorless crystals can be obtained by recrystallisation from EtOAc: M.p. $183-5^\circ$; $[\alpha]_D^{25} +52.6^\circ$ (c 0.53 MeOH); ¹H NMR (400 MHz, DMSO-d₆) δ 10.04 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.26-7.33 (m, 4H), 7.19 (t, J = 7.1 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.00 (s, 2H), 6.88 (s, 1H), 4.33 (m, 1H), 3.00 (dd, J = 4.5, 13.4 Hz, 1H), 2.84 (dd, J = 10.0, 13.4 Hz, 1H), 1.32 (s, 9H); MS (FAB) m/z 439 (MH)⁺; Anal. Calcd for $C_{23}H_{26}N_4SO_3$: C, 62.99; H, 5.98; N, 12.78. Found: C, 62.69; H, 5.99; N, 12.65.

Example 12

15

20

10

5

 $N-\{4-(2-A\min o-4-thiazolyl) \text{ phenyl}\}-5-oxo-1-$ (phenylmethyl)-2(R)-pyrrolidinecarboxamide (1: R¹ = NH₂, R² = H, R³ and R⁴ together form a CH₂CH₂C(O) group and R⁵ = PhCH₂, and the carbon atom bearing R³ has the (R)configuration)

a) N-(Phenylmethyl)glutamic acids {(R) and (S)}:
N-(Phenylmethyl)glutamic acids were prepared using known procedures (P. Quitt, J. Hellerbach, K.

Vogler, Helv. Chim. Acta, 1963, 46, 327 and J.S. Petersen, G. Fels, H. Rapoport, J. Am. Chem. Soc., 1984, 106, 4539) with a minor modification. The solid obtained by precipitation of N-(phenylmethyl)glutamic acid from the aqueous reaction mixture at the isoelectric point (pH 3-4) was not dried as described but used as such in the next step.

- 71 -

5

10

15

MEDOCID, MO

b) 5-Oxo-1-(phenylmethyl)-2-pyrrolidinecarboxylic acids $\{2(R) \text{ and } 2(S)\}$: 5-Oxo-1-(phenylmethyl)-2-pyrrolidinecarboxylic acids $\{2(R) \text{ and } 2(S)\}$ were prepared according to a known procedure (J.S. Petersen, G. Fels, H. Rapoport, J. Am. Chem. Soc., 1984, 106, 4539) and gave colorless oils which crystallized on standing and were sufficiently pure to be used in the next step. For example, (D)-glutamic acid (50 g , 340 mmol) produced the title compound (2(R); 27.66 g, 37% yield): $[\alpha]_D^{25}$ -47.4° (c 1.29 MeOH); ¹H NMR (400 MHz, CDCl₃) δ 8.2 (broad s, 1H), 7.19-7.38 (m, 5H), 5.16 (d, J = 15.2 Hz, 1H), 4.02 (dd, J = 9.5, 2.9 Hz, 1H), 3.98 (d, J = 15.2 Hz, 1H), 2.55-2.69 (m, 1H), 2.43-2.54 (m, 1H), 2.24-

The title compound: To an ice-cold solution of C) 5-oxo-1-(phenylmethyl)-2(R)-pyrrolidinecarboxylic acid (13.81 g, 62.99 mmol) in dry THF (126 mL) under 20 nitrogen were added N-methylmorpholine (8.3 mL, 75.58 mmol) and isobutyl chloroformate (9.0 mL, 69.29 mmol). The mixture was stirred at 0° for 304-(4-Aminophenyl)-2-thiazolamine (12.05 g, 62.99 mmol) was added to the mixture. The reaction 25 mixture was allowed to warm to room temperature and was stirred for an additional 19 h. The mixture was diluted with EtOAc (500 mL) and the resulting solution was extracted with 10% aqueous HCl (2 \times 250 mL). The aqueous phase was rendered basic (pH = 12) with 10 N aqueous NaOH and extracted with EtOAc. 30 This organic phase was washed with brine, dried (MgSO₄) and concentrated under reduced pressure to afford an orange solid (21.72 g). Purification by

2.36 (m, 1H), 2.11-2.22 (m, 1H).

flash chromatography (SiO₂, EtOAc:MeOH, 1:0 to 10:1) followed by recrystallisation from ethanol yielded the title compound as a pale yellow solid (5.66 g, 23% yield): M.p. 245-6°; $[\alpha]_D^{25}$ +123.6 (c 1.006 MeOH); ¹H NMR (400 MHz, DMSO-d₆) δ 10.14 (s, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.21-7.35 (m, 5H), 7.01 (s, 2H), 6.90 (s, 1H), 4.90 (d, J = 15.3 Hz, 1H), 4.11 (dd, J = 8.7, 3.3 Hz, 1H), 3.79 (d, J = 15.2 Hz, 1H), 2.25-2.47 (m, 3H), 1.93-1.99 (m, 1H); MS (FAB) m/z 393 (MH)⁺; Anal. Calcd for $C_{21}H_{20}N_4OS_2$: C, 64.27; H, 5.14;, N, 14.27. Found: C, 63.45; H, 5.16; N 14.17.

15 Example 13

20

25

30

tert-Butyl 2(S)-{{ $4-(2-Amino-4-thiazolyl)phenyl}$ -amino}carbonyl}-1-pyrrolidinecarboxylate (1: R^1 = NH_2 , R^2 = H, R^3 and R^4 together form a $CH_2CH_2CH_2$ group and R^5 = Boc, and the carbon atom bearing R^3 has the (S)configuration)

To (L)-Boc-proline (935 mg, 4.35 mmol) in dry THF (9 mL) were added successively 4-(4-aminophenyl)-2-thiazolamine (831 mg, 4.35 mmol), DIPEA (2.3 mL, 13.04 mmol) and TBTU (1.535 g, 4.79 mmol). The mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated under reduced pressure. The residue thus obtained was diluted with EtOAc and extracted with 10% aqueous HCl. The resulting aqueous phase was rendered basic (pH = 12) with 10 N aqueous NaOH and extracted with EtOAc. The organic extract was dried (MgSO₄) and

- 73 -

concentrated under reduced pressure. Purification by flash chromatography (SiO2, EtOAc) afforded the desired product (1.04 g, 62% yield) as an off-white solid which could be used as such in the next 5 transformation or further purified by recrystallisation from EtOAc-MeOH to give a white solid: M.p. 238-239°; $\{\alpha\}_{D}^{25}$ -33.6 (c 1.03 DMSO); $^{1}_{H}$ NMR (400 MHz, DMSO-d₆) δ (2 : 1 mixture of rotamers) 9.98 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.59 (d, J =8.4 Hz, 2H), 7.00 (s, 2H), 6.88 (s, 1H), 4.19 (maj.) 10 and 4.26 (dd, J = 8.1, 4.5 Hz and d, J = 6.6 Hz, 1H), 3.30-3.45 (m, 2H), 2.15-2.25 (m, 1H), 1.75-1.95 (m, 3H), 1.27 (maj.) and 1.40 (2s, 9H); MS (FAB) m/z389 (MH)+; Anal. Calcd for $C_{19}H_{24}N_4O_3S$: C, 58.74; H, 6.23; N, 14.42. Found: C, 58.35; H, 6.26; N, 14.35. 15

Example 14

N-{4-(2-Amino-4-thiazolyl)phenyl}-1-benzoyl-2(S)pyrrolidinecarboxamide: (1: $R^1 = NH_2$, $R^2 = H$, R^3 and R^4 together form a $CH_2CH_2CH_2$ group and $R^5 = H$, and the carbon atom bearing R^3 has the (S) configuration)

25

30

a) $N-\{4-(2-A\min o-4-thiazolyl) phenyl\}-2(S)-pyrrolidinecarboxamide: Trifluoroacetic acid (5 mL) was added to a solution of the title compound of example 13 (610 mg, 1.57 mmol) in <math>CH_2Cl_2$ (20 mL). The mixture was stirred at room temperature for 1.5 h. The mixture was then diluted with EtOAc and the resulting solution was washed with 2 N aqueous NaOH and brine, then was dried (MgSO₄) and concentrated

10

15

20

25

30

under reduced pressure to afford the desired product (400 mg, 88% yield) as a beige foam: 1 H NMR (400 MHz, DMSO- d_{6}) δ 9.96 (s, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 6.99 (s, 2H), 6.89 (s, 1H), 3.69 (dd, J = 8.8, 5.6 Hz, 1H), 2.90 (t, 2H, J = 6.6 Hz), 2.69 (s, 1H), 2.00-2.10 (m, 1H), 1.74-1.83 (m, 1H), 1.65 (quint., 2H, J = 6.9 Hz).

The title compound: The product of preceding section a) (200 mg, 0.694 mmol) was dissolved in dry THF (3.5 mL). Benzoic acid (85 mg, 0.694 mmol), Nmethylmorpholine (153 μ L, 1.39 mmol) and TBTU (245 mg, 0.763 mmol) were added to the solution. mixture was stirred at room temperature for 1.5 h, and then concentrated under reduced pressure. residue was dissolved in EtOAc. The solution was extracted with 10% aqueous HCl. The aqueous phase was rendered basic (pH 12) with 10% aqueous NaOH and then extracted with EtOAc. The extract was dried (Na₂SO₄) and concentrated under reduced pressure to afford a yellow oil. The oil was purified by flash chromatography (SiO2, EtOAc) and then lyophilized from acetonitrile-H2O to afford the title compound (141 mg, 52% yield) as an off-white solid of >96.5% purity (containing acetonitrile): Mp 132-133°; $[\alpha]_n^{25}$ -122.3 (c 1.00, MeOH); ¹H NMR (400 MHz, DMSO-d₆), (4:1 mixture of rotamers), δ 10.10 (major) and 9.74 (s, 1H), 7.74 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H)Hz, 2H), 7.65-7.70, 7.55-7.57 and 7.33-7.37 (m, 5H), 6.99 (s, 2H), 6.89 (major) and 6.87 (s, 1H), 4.60 (major) and 4.38 [(dd, J = 7.9, 5.2 Hz) and (d, J =7.1 Hz), 1H], 3.49-3.69 (m, 2H), 2.20-2.35 (m, 1H), 1.80-2.00 (m, 3H); MS (FAB) m/z 393 (MH)+; Anal.

- 75 -

Calcd for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.27. Found: C, 61.64; H, 5.34; N, 14.50.

5 Example 15

 $N-\{4-(2-Amino-4-thiazoly1) phenyl\}-1-(phenylmethyl)-2(S)-pyrrolidinecarboxamide (1: <math>R^1=NH_2$, $R^2=CH_3$, R^3 and R^4 together form a $CH_2CH_2CH_2$ group and $R^5=PhCH_2$, and the carbon atom bearing R^3 has the (S) configuration)

The title compound (573 mg, 31% yield) was prepared from (L)-N-(phenylmethyl)proline (1.00 g, S. W. 15 Goldstein, L. E. Overman, M. H. Rabinowitz, J. Org. Chem. 1992, 57, 1179) and 4-(4-aminophenyl)-2thiazolamine using the procedure described for the tert-butyl carboxylate derivative in example 13. The title compound had m.p. 207-9°; $[\alpha]_D^{25}$ -88.7 (c 1.00 CHCl₃); ¹H NMR (400 MHz, DMSO-d₆) δ 9.69 (s, 20 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 6.9 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 6.99 (s, 2H), 6.89(s, 1H), 3.84 (d, J = 12.9 Hz, 1H), 3.60 (d, J =25 12.9 Hz, 1H), 3.24 (dd, J = 9.3, 4.8 Hz, 1H), 3.01-3.06 (m, 1H), 2.40 (q, J = 8.4 Hz, 1H), 2.11-2.21 (m, 1H), 1.72-1.89 (m, 3H); MS (FAB) m/z 379 (MH)+; Anal. Calcd for $C_{21}H_{22}N_4OS$: C, 66.64; H, 5.86; N, 14.80. Found: C, 66.24; H, 5.77; N, 14.48.

30

10

Example 16

The following four assays (A, B and Ci and Cii) were used to evaluate antiherpes activity, and a fifth assay (D) was used to measure the stabilization of the DNA-herpes helicase-primase interaction.

A) HSV-1 DNA-Dependent ATP Assay (an in vitro assay based on the inhibition of HSV-1 helicase-primase).

10

15

20

5

- a) Preparation of enzyme: HSV-1 helicase-primase holoenzyme was produced in triply infected Sf21 cells using recombinant baculoviruses expressing the UL5, UL8 and UL52 helicase-primase subunits, as described by S. Dracheva et al., J. Biol. Chem. 1995, 270, 14148. The crude enzyme was purified by ammonium sulfate precipitation, Source 15Q® chromatography and Sephacryl® S-300 HR gel filtration (both purification systems can be obtained from Pharmacia Biotech Inc., Montreal, Quebec, Canada), see S. Dracheva et al., supra.
- b) Assay: The DNA-dependent ATPase assay, described by J.J. Crute et al., Nucleic Acids Res. 1988, 16,
 25 6585, was modified and used to evaluate the capability of the compounds of Group 1-formula 1 to inhibit HSV-1 helicase-primase activity. The reaction mixtures (80 μL each) contained 40 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, pH 7.5), 10% (v/v) glycerol, 5.5 mM MgCl₂, 1 mM DL-dithiothreitol (DTT), 50 μg/mL acetylated bovine serum albumin, 3.3% (v/v) DMSO, 4 mM ATP, 25 μM single-stranded M13 DNA hybridized to double-tailed 68-mer oligonucleotide and 3 μg/mL HSV-1

- 77 -

helicase-primase. After incubation for 20 min at 34°, formation of inorganic phosphate from hydrolysis of ATP was monitored spectrophotometrically at 650 nm using acidic ammonium molybdate/malachite green reagent, P.A. Lanzetta et al., Anal. Biochem. 1979, 100, 95. DNA-dependent ATPase activity was calculated from the net absorbance change in the presence and absence of inhibition.

10

5

B) Inhibition of Herpes Simplex Virus (HSV-1) Replication in Cell Culture

Assay: BHK-21 cells clone 13 (ATCC CCL10) were incubated for two days in 850 cm2 roller bottles 15 $(2x10^7 \text{ cells/bottle})$ with $\alpha\text{-MEM}$ medium (Gibco Canada Inc., Burlington, Ontario, Canada) supplemented with 8% (v/v) fetal bovine serum (FBS, Gibco Canada, The cells were trypsinized and then 3,000 20 cells in 100 μ L of fresh medium were transferred into each well of a 96-well microtiter plate. cells were incubated at 37° for a period of 3 days to reach a density of 50,000 cells per well. cells were washed twice with 100 μL of $\alpha\text{-MEM}$ 25 supplemented with 2% heat inactivated FBS and incubated for 1-2 hours in 100 μL of the same medium.

Thereafter, the cells were infected with HSV-1 strain F or KOS (multiplicity of infection = 0.05 PFU/cell) in 50 μ L of α -MEM supplemented with 2% heat inactivated FBS. Following one hour of virus absorption at 37°, the medium was removed and the cells were washed with α -MEM supplemented with 2%

25

heat inactivated FBS (2 x 100 μ L). The cells were incubated with or without 100 μ L of the appropriate concentration of test reagent in α -MEM medium supplemented with 2% heat inactivated FBS. After 24 hours of incubation at 37°, the extent of viral replication was determined by an ELISA assay; for instance, the following assay that detects the late glycoprotein C of HSV-1.

- 10 Cells were fixed in the microtiter plate with 100 μL of 0.063% glutaraldehyde in phosphate buffered saline for 30 min at room temperature. microtiter plate was then washed once with casein blocking solution and blocked with 200 µL of the 15 same solution for one hour at room temperature. Thereafter, 100 µL of mAb C11 recognizing the glycoprotein C of HSV-1 (see E. Trybala et al., Journal of General Virology, 1994, 75, 743) was added to each well for two hours at room 20 temperature. The plate was washed three times with phosphate buffered saline containing 0.05% polyoxyethylene (20) sorbitan monooleate. The cells were incubated with 100 µL of sheep anti-mouse IgG horseradish peroxidase for one hour at room
- The plate was washed three times with 200 µL of the above-noted phosphate buffer saline preparation, and then once with 0.1 M sodium citrate (pH 4.5).

 Thereafter, 100 µL of orthophenylenediamine dihydrochloride (OPD, Gibco, Canada Inc.) was added to each well. The plate was agitated on a microplate shaker for 30 min in the dark. Color

temperature in the dark.

- 79 -

development was monitored at 450 nm using a microplate spectrophotometer.

SAS was used to calculate % inhibition of viral replication and to generate EC_{50} values.

- C) Inhibition of Human Cytomegalovirus (HCMV) replication
- The effect of compounds on the replication of HCMV has been measured by using an ELISA-based assay (ELISA) and a plaque reduction assay (PRA).
 - Ci) ELISA ASSAY:

Hs-68 cells (ATCC # CRL 1635) were seeded in 96 well microtiter plates at 10,000 cells/well in 100 µL of DMEM medium (Gibco Canada Inc.) supplemented with 10% fetal bovine serum (FBS, Gibco Canada Inc.).

- The plates were incubated for 3 days at 37° to allow the cells to reach 80-90% confluency prior to the assay.
- The medium was removed from wells by aspiration.

 The cells then were infected at a multiplicity of infection (MOI) of 0.01 PFU/cell with 50 µL of HCMV (strain AD169, ATCC VR-538) in DMEM medium supplemented with 5% heat inactivated FBS (assay medium). The virus was allowed to adsorb to cells for 2 h at 37°. Following viral adsorption, the medium was removed from the wells by aspiration. The cells were washed twice with 200 µL of assay

- 80 -

medium to remove unabsorbed virus. The cells were then incubated with or without 100 μL of appropriate

concentrations of test reagent in assay medium. After 8 days of incubation at 37°, the extent of viral replication was determined by an ELISA assay which detects the late structural protein p28 of HCMV.

Eight days after infection, the medium was aspirated from the wells. Non-specific binding sites were blocked by adding 200 μL of phosphate buffered saline containing 1% (w/v) bovine serum albumin 10 (blocking buffer) to each well and incubating the plates for 30 min at room temperature. After removal of the blocking buffer by aspiration, the cells were fixed with 100 μL of cold ethanol-acetone 15 solution (95:5) per well. The plates were placed at -20° for 30 min. The plates were washed 4 times with phosphate buffered saline containing 0.05% (v/v) polyoxyethylene sorbitan monolaurate (Tween 20 Thereafter, 100 µL of mAb UL99 (Advanced 20 Biotechnologies Inc., # 13-130-100) recognizing HCMV protein p28 was added to each wells and plates were incubated for 2 h at room temperature. The plates were washed four times with 200 µL of the abovenoted phosphate buffered saline/Tween-20® solution. 25 The cells were then incubated with 100 µL of sheep anti-mouse IgGy horseradish peroxidase conjugated for 2 h at room temperature. The plates were then washed four times with 200 µL of above-noted phosphate buffered saline/Tween-20® solution. 30 Thereafter, 100 µL of ortho phenylenediamine dihydrochloride (OPD, Gibco Canada Inc.) solution was added to each well and the plates were agitated on a microplate shaker for 30 min in the dark.

- 81 -

Color development was monitored at 450 nm using a microplate spectrophotometer.

The SAS program was used to calculate the % inhibition of viral replication and to generate EC₅₀ values.

The EC₅₀ values obtained according to this assay method for certain thiazolylphenyl derivatives of this invention are listed in the following tables under the heading ELISA CMV.

Cii) PRA ASSAY:

10

25

30

Hs-68 cells (ATCC # CRL 1635) were seeded in 12well plates at 83,000 cells/well in 1 mL of DMEM medium (Gibco Canada Inc.) supplemented with 10% fetal bovine serum (FBS, Gibco Canada Inc.). The plates were incubated for 3 days at 37° to allow the cells to reach 80-90% confluency prior to the assay.

The medium was removed from the cells by aspiration. The cells were then infected with approximately 50 PFU of HCMV (strain AD169, ATCC VR-538) in DMEM medium supplemented with 5% inactivated FBS (assay medium). The virus was allowed to adsorb to cells for 2 h at 37°. Following viral adsorption, the medium was removed from the wells by aspiration. The cells were then incubated with or without 1 mL of appropriate concentrations of test reagent in assay medium. After 4 days of incubation at 37°, the medium was exchanged with fresh medium containing test compound and 4 days later the cells were fixed with 1% aqueous formaldehyde and stained with a 2%

15

20

crystal violet solution in 20% ethanol in water.

Microscopic plaques were counted using a
stereomicroscope. Drug effects were calculated as a
percent reduction in the number of plaques in the
presence of each drug concentration compared to the
number observed in the absence of drug. Ganciclovir
was used as a positive control in all experiments.

The EC₅₀ values obtained according to this assay for certain thiazolyl derivatives of this invention are listed in the following tables under the heading PRA CMV.

D) HSV-1 Helicase-primase-DNA stabilization assay

The following represents a preferred protocol which was used for designing single-stranded fluorescently labeled DNA substrate to measure the stabilization of the DNA-herpes helicase-primase interaction (Tenney, D.J., Scheaffer, A.K., Hurlburt, W.W.,

Bifano, M., and Hamatake, R.K. (1995) J. Biol. Chem., 270, 9129-9136):

A foldback 86-mer oligonucleotide designed to mimic a replication fork-like structure was prepared, where one nucleic acid base was replaced with fluorescein using phosphoramidite chemistry. An example of such a substrate is 5'
CCAACGTCCFGTATAATGAGGTACCCGGGGATCCTCTAGGATATATCC
TAGAGGATCCCCGGGTACGGTATAATGAGCCAGTTCTT-3', where F:

TAGAGGATCCCCGGGTACGGTATAATGAGCCAGTTCTT-3', where F = fluorescein. Other oligonucleotide sequences may be used as long as the secondary structure (replication fork) is maintained. The fluorescent probe may be located anywhere within the sequence, except at

- 83 -

either the 5' or 3' ends. Single stranded oligonucleotides containing the primase consensus binding site may also be used. An example of such a substrate is 5'-CCAACGTCCCTACCCTCCCGAFTATAATGAG-3', where **F** = fluorescein. Other sequences containing the primase consensus binding site (CCCTCCCGA) may be used. The fluorescent probe may be located anywhere within the sequence, except at either the 5' or 3' ends or within the primase binding site.

10

15

20

5

Solutions for fluorescence anisotropy analysis (2mL total) contained 40mM 4 - (2 - hydroxyethyl) - 1 piperazineethanesulfonic acid (HEPES, pH 7.5), 10% (v/v) glycerol, 5.5mM MgCl₂, 1mM DL dithiothreitol (DTT), 0.1% - 3.0% (v/v) DMSO, 100 μ M ATP γ S, 150 μ M NaCl, 25 nM fluorescein-labeled oligonucleotide, 250 nM helicase-primase (UL5/UL52 subassembly). Fluorescence anisotropy was measured through a LG-530 filter (Corion) using an excitation wavelength of 490nm. Anisotropy values were converted to fraction oligonucleotide bound to enzyme in the presence and absence of inhibitor. Stabilization of enzyme-DNA complex by an inhibitor was demonstrated by an increase in fraction oligonucleotide bound.

25

30

The effect was further characterized by measuring the binding affinities of oligonucleotide for enzyme in the presence and absence of inhibitor. The solutions (2mL total) contained 40mM HEPES, pH 7.5, 10 % (v/v) glycerol, 5.5mM MgCl₂, 1mM DL dithiothreitol (DTT), 0.1% - 3.0% (v/v) DMSO, 100 μ M ATP γ S, 150mM NaCl, 25 nM fluorescein labeled oligonucleotide. Aliquots of helicase-primase (UL5/UL52 subassembly) were added and fluorescence

anisotropy was measured after each addition until no further anisotropy change was observed. Nonlinear regression analysis was used to calculate dissociation constants from the anisotropy values for enzyme binding to oligonucleotide in the presence and absence of inhibitor.

Examples of results obtained in accordance with this assay for two thiazolyphenyl derivatives are illustrated in Figure 5. The two derivatives are N-{2-{4-(2-amino-4-thiazolyl)phenyl}amino}-2-oxoethyl}-N-(4-pyridinylmethyl)cyclohexane-carboxamide(Entry No. 49 of Table 1 of Group 1) and N-{2-{4-(2-amino-4-thiazolyl)phenyl}amino}-2-oxoethyl}-N-(phenylmethyl)-4-pyridinecarboxamide (Entry No 29 of Table 1 of Group 1).

Example 17

20

25

In conjunction with the appropriate starting materials and intermediates, the procedures of Group 1-examples 1 to 15 can be used to prepare other compounds of Group 1-formula 1. Examples of compounds thus prepared are listed in Tables 1 to 6 of Group 1-example 17, together with mass spectrum data for the individual compounds and the results obtained from three assays demonstrating antiherpes activity.

30

(Symbols used in the following Group 1 tables, and in subsequent tables, include 4-ClPh: 4-chlorophenyl; 4-Cl-3-IPh: 4-chloro-3-iodophenyl; 2-FPh: 2-fluorophenyl; 3-FPh: 3-fluorophenyl; 4-FPh:

- 85 -

```
4-fluorophenyl; (4-Me<sub>2</sub>NPh)CH<sub>2</sub>: {4-(dimethylamino)-phenyl}methyl; 2-MePh: 2-methylphenyl; 4-MePh: 4-methylphenyl; 2,6-Me<sub>2</sub>Ph: 2,6-dimethylphenyl; 4-MeOPh: 4-methoxyphenyl; 5-Cl-2-MeOPh: 5-chloro-2-methoxyphenyl.)
```

TABLE 1	of formula 1 having the structure $\begin{bmatrix} R^2 \\ $	$R^1 \longrightarrow N \longrightarrow 0 \qquad R'$ in R^1 is NH2, R^2 and R^3 are each H, Q is absent and R^4 and R^5 are designated llows:	· · · · · · · · · · · · · · · · · · ·	(µм) (µм) EC ₅₀ (µм)	H PhCH ₂ 339 6.4 2.7 25 >60	H PhCH ₂ CH ₂ 353 4.7 6 3.1	H PhCH ₂ CH ₂ CH ₂ 367 7.6 18 1.8 >14*	H (4-FPh)CH ₂ 357 3.5 1.8 16	H (4-C1Ph)CH ₂ 373/375 ^{**} 5.4 42	H (4-MePh)CH ₂ 353 19 18	H (4-MeOPh) CH ₂ 369 48 7
		wherein \mathbb{R}^1 is as follows:	•	R4	н	н	н	Н	н	Ħ	E
		HZFKX		o N	1	2	3	4	5	9	7

- 87 -

			TABLE 1				
Entry No	R4	R5	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀ (μM)	HSV-1 EC ₅₀	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
œ	##	CH ₂	345	2.9	œ	3.6	Cart
6	Н	(3-FPh)CH ₂		ca.5			
10	Н	Ph- (S)-СНМе	353	6.9	2.2	2.2	>30*
11	н	Ph- (R)-CHMe	353	3.7	1.3	19	19
12	x	N CH ₂	340	ω	1.5		84*
13	Н	S CH ₂	345	3.8	3.7	8.3	
14	н	O NCH ₂ CH ₂	362	7.7	3.2	67	
15	PhCH ₂	Me	353	3.3	0.95	6.2	6.5

- 88 -

			TABLE 1 (continued)				
Entry No	R4	R5	FAB/MS (m/z) (MH) +	HSV-1 IС ₅₀ - (µМ)	HSV-1 EC ₅₀ (μΜ)	ELISA CMV EC ₅₀ (µM)	PRA CMV EC ₅₀ (µM)
16	PhCH ₂	PhCH ₂	429	0.55	0.45	3.8	13
17	(2-FPh)CH2	(2-FPh)CH ₂		1.8	4.0		
18	(3-FPh)CH ₂	(3-FPh) CH ₂		0.4	0.1		
19	Н	C (0)	354	13	4.5		20
20	н	(0) C(0)		23			09
21	н	C (0)		4.2	1.3		>71
22	Ме	(C (O)	368	5.9	1.8	110	110*
23	PhCH2	Phc (0)	443	0.072	0.007	12	36

- 89 -

	1	T		7			1	
	PRA CMV EC ₅₀	(pm)		15	>36*	35	27	×88
	ELISA CMV EC50	14	4.4	1.8	7	4.6	12	77
	HSV-1 EC ₅₀ (μΜ)	0.002	0.011	0.05	0.28	0.13	0.035	0.43
	HSV-1 IC ₅₀ (µМ)	0.048	0.047	0.5	1.0	0.43	0.24	0.44
TABLE 1	FAB/MS (m/z) (MH)+	461	471	455	444	444	444	460
	R5	(4-FPh)C(0)	(2,6-Me ₂ Ph)C(0)	PhCH ₂ C(0)	C(0)	C(0)	C (0)	- O C (0)
	R4	PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂	РhСН ₂	РhСн ₂
	Entry No	24	25	26	27	28	29	30

- 90 -

	PRA CMV EC ₅₀ (µM)	8.1	8.5	20	15		16
	ELISA CMV EC ₅₀ (μΜ)	1.3	5.4	28.2	1	8.1	2.8
	HSV-1 EC ₅₀ (µM)	0.4	0.04	0.17	0.004	0.006	0.005
	HSV-1 IC ₅₀ (µM)	1.6	0.42	1.1	0.026	0.035	0.041
TABLE 1 (continued)	FAB/MS (m/z) (MH) +	458	449	445	449	463	435
	R5	(O) CH ² C(O)	(S) C(O)	$\left(\frac{N}{N} \right)^{C(0)}$	(0)2-	$\left\langle \sum_{CH3} C(0) \right\rangle$	C (0)
	R4	PhCH2	PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂
	Entry No	31	32	33	34	35	. 36

- 91 -

TABLE 1 (continued)	FAB/MS HSV-1 HSV-1 ELISA PRA (m/z) IC ₅₀ EC ₅₀ CMV CMV (MH) + (μM) (μM) (μM) (μM) (μM)		(A) -CH ₂ C(O) 463 0.088 0.016 4 4.6	CH ₂ C(0) 449 0.059 0.009 6.1 8.5	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Me ₃ CC(0) 423 0.80 0.036 14 34) 437 0.026 0.002 6	Me ₂ CHC(0) 409 1.6 0.13 25 13	MeC(0) 381 3.3 0.75 16 37
		37 PhCH ₂ C(0)	38 PhCH ₂ CH ₂ C(0)	39 PhCH ₂ CH ₂ C (0)		PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂
	Z	m	m	3.	4	41	42	43	44

			TABLE 1 (continued)				
Entry No	R4	R5	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀ (µМ)	HSV-1 EC _{SO} (µM)	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
45	(4-C1Ph)CH ₂	(o) D	483/485**	0.050	0.001		5.5
46	(4-MeOPh) CH ₂	(0)D	479	0.075	0.094	8	
47	N CH ₂	(o)	450	0.072	0.013	19	>103
48	N CH2	C(0)	450	0.14	0.04	S	49
49	CH ₂	C(0)	450	0.037	0.012	25	23

- 93 -

Putry			TABLE 1 (continued)				
No	R4	R5	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀ (µМ)	HSV-1 EC ₅₀ (µM)	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
20	CH ₂ CH ₂	(o)	464	9.0	0.068	1.6	13
51	S CH2	(0)	455	0.063	0.002	9	11
52	Ph- (R)-CHMe	(o)	463	0.087	0.013	1.3	9
53	Ph- (<i>S)</i> -СНИе	c (o)	463	0.038	0.003	3.2	12
54	O NCH ₂ CH ₂	(o)	466	16	3.5	31	.63
55	(4-C1Ph)CH2	N	478/480**	0.57	0.095	11.9	
					7		

	PRA CMV EC ₅₀ (µM)		15.8	30		15	·
	ELISA CMV EC ₅₀ (µM)	38	2.6	5.2		3	
	HSV-1 EC ₅₀ (µМ)	0.55	0.95	0.04	0.015	0.54	1.6
	HSV-1 IC ₅₀ (µМ)	1.2	3.9	0.19	08.0	1.5	4.4
TABLE 1 (continued)	FAB/MS (m/z) (MH) ⁺	445	450	458	461	449	556
	R ⁵	N	(O) D—C	(O) D—(N	(o) 24d	Phc (0)	Boc-N - C(0)
	R4	CH2 CH2	CH2	Ph- (<i>S)</i> -СНМе	(4-FPh) CH ₂	CH2	CH2
	Entry No	26	57	28	59	09	61

- 95 -

						
	PRA CMV EC50	38	>21*	20		>10
	ELISA CMV EC50	(µM) 2.2	2.2	0.75		0.35
	HSV-1 EC ₅₀	i	0.25	1.7		0.090
	HSV-1 IC ₅₀	29% inhi- bition at 50 µM	0.78	2.5	0.84	0.40
TABLE 1	FAB/MS (m/z) (MH) +	456	441	450	519	449
	R.5	HN — C (0)	(o)	(O) C (O)	N ₃ —C(0)	C(0)
	R4	CH ₂	CH2	COH2	(4-C1Ph)CH ₂	PhCH ₂ CH ₂
	Entry No	62	63	64	65	99

- 96 -

	·	,	,		,		,	·
	PRA CMV EC ₅₀ (µM)	93		æ		>32	24	
	ELISA CMV EC ₅₀ (µM)	2.1	>5				7.5	12.6
	HSV-1 EC ₅₀ (μM)	0.21	0.05	0.18	0.16		0.67	0.017
	HSV-1 IC ₅₀ (μM)	0.35	0.18	0.43	0.57	30	0.65	0.088
TABLE 1 (continued)	FAB/MS (m/z) (MH)+	458	463	497	478/480**	396	496	462
	R5	NS C (0)	(O) D-C(O)	(O)2 ^Z HD-	C (0)	$NH_2CH_2C(0)$	Me ₃ COC(0)-NHCH ₂ C(0)	(4-FPh)C(O)
	R4	PhCH ₂ CH ₂	PhCH ₂ CH ₂	(4-C1Ph)CH ₂	(4-C1-3-IPh)CH ₂	PhCH ₂	PhCH ₂	N CH ₂
	Entry No	<i>L</i> 9	89	69	70	71	72	73

- 97 -

PCT/US96/19131

	ELISA PRA CMV CMV EC ₅₀ EC ₅₀ (uM)		48	25	6.1 7.5		3.8 55
	HSV-1 EC ₅₀ (µM)	0.12	0.24	0.16	0.19	0.18	0.16
	HSV-1 IC ₅₀ (µM)	0.28	0.21	0.08	0.37	-	0.84
TABLE 1 (continued)	FAB/MS (m/z) (MH) +	484	455	469	464	485	450
	R5	N ₃ —C(0)	CH ₂ C(0)	CH2C(0)	РhСH ₂ C (0)	N_3 —C(0)	(0)
	R4	PhCH ₂	CH ₂	CH2	Cap Cap	N CH2	(N CH2CH2
	Entry No	74	75	76	77	78	79

			TABLE 1				
Entry No	R4	R.5	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀ (µM)	HSV-1 EC ₅₀	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
80	Me ₃ CCH ₂	(o) D—c (o)	429	96.0	0.31	9.5	9.5
81	Ме ₂ СНСН ₂	(0) D—C (0)	415	0.48	0.18	14	
82	Pr ₂ CH	(o) 2—C	457	0.62	0.060	8.1	1*
83	(4-FPh)CH ₂	(0)2—C	467	0.042	0.006	8.1	
84	(4-FPh)CH ₂	N	462	0.36	0.14	5.6	.37
85	PhCH ₂	Me ₃ COC (O)	439	0.016	0.010	9.0	12
98	PhCH ₂	Me ₂ CHCH ₂ OC(0)	439	0.17	0.088	3.8	24
87	PhCH ₂	MeOC (0)	397	2.8	1.1	18	
88	Ph-(R)-CHMe	Me ₃ COC (0)	453	2.4	1.2	>47	

- 99.~

TABLE 1	5 (MH) + (μM) (μM) (μM) (μM) (μM) (μM)	453 0.098 0.036 0.9	440 0.058 0.015 3.5	C(0) 473/475** 0.070 0.025 1 6	438 0.076 0.034	454 0.16 0.12 0.25	452 0.026 0.065 >8	452 0.14 0.037 57	S(0) ₂ 488 0.29 0.12 0.35 12	0)2 479 0.31 0.13 >5 15
	HSV-1 IC ₅₀ (µM)	0.098	0.058	┷	0.076	0.16	0.026	0.14	0.29	0.31
TABLE 1	FAB/MS (m/z) (MH) +	453	440	473/475**	438	454	452	452	488	479
	R ⁵	Me ₃ COC(0)	Me ₃ COC (0)	Me ₃ COC (0)	Me ₃ CNHC(0)	Me ₃ CNHC(S)	Me ₃ CN (Me) -C(0)	O NC (0)	0 NS (0) 2	PhS (0) ₂
	R4	Ph-(S)-CHMe	N CH2	(4-C1Ph)CH ₂	PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂
	Entry	88	06	91	92	93	94	95	96	97

	1				
	PRA CMV EC ₅₀ (µM)		·		
	ELISA CMV EC ₅₀ (µM)	>3		14	1.9
	HSV-1 EC ₅₀ (µM)	2.1	0.67	0.85	0.74
1	HSV-1 IC ₅₀ (μΜ)	0.5	1.6	0.76	2.2
TABLE 1 (continued)	FAB/MS (m/z) (MH) +	572	573	445	454
		S(0) ₂	S(O) ₂	Me3COC(0)	Me ₃ COC(O)
	R4	PhCH ₂	N CH2	CH2	$\left\langle \begin{array}{c} N \\ - \end{array} \right\rangle$ CH ₂ CH ₂
	Entry No	86	66	100	101

- 101 -

			TABLE 1				
Entry No	R4	R ⁵	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀ (µM)	HSV-1 EC ₅₀	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
102	(2-MePh)CH ₂	NC (0)	458	0.19	0.011	11	(MM) 18
103	CH2CH2	c(0)	469	0.15	0.24	>41	
104	PhCH ₂	Et2CHC(0)	437	0.078	0.016	1.9	>18*
105	Ph-(S)-CHMe	Me ₃ CNHC(0)	452	0.7	0.29	11	
106	PhCH ₂	Me2NS(0) ₂	446	1.0	0.16	9<	
107	CH ₂	0 N-S(0)2	494	2.6	0.83	1.1	12*
108	(S)-CHMe	Me ₃ COC(0)	459	0.46	0.39	6.8	
109	PhCH ₂	PhCH ₂ OC (0)	473	0.31	0.2	>20	
110	Me ₂ CHCH ₂	PhCH ₂ OC (0)	439	3.2	1.6	>40	
111	Pr ₂ CH	Me ₃ COC (0)	447	0.37	0.24	4.0*	
							-

	A PRA CMV EC ₅₀		>50*	23	49	19	35
	ELISA CMV EC ₅₀ (µM)	3.2					
	HSV-1 EC ₅₀ (μΜ)	1.2	·				
	HSV-1 IC ₅₀ (µМ)	1.8	2.0	0.80			
TABLE 1 (continued)	FAB/MS (m/z) (MH) +	405	458	458	449	463	463
	R5	Me ₃ COC (O)	(O)2°H2 (O)	CH ₂ C(0)	(c))	(C) CH2C(O)	(O)2 ^z H2 (O)
	R4	Ме ₂ СНСН ₂	PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂	PhCH ₂
	Entry No	112	113	114	115	116	117

- 103 -

3LE 1 tined)	M (μM) (μM) (μM) (μM) (μM) (μM) (μM) (μM	0.047	479 0.68 25	173 0.54 15	501 0.49
	HSV-1 IC ₅₀ (μM)	0.047	0.68	0.54	0.49
TABLE 1	FAB/MS (m/z) (MH) +	462	479	473	501
	R5	(C(O)	H ₂ N CH ₂ C(0)	(0)2-тоо	Me OCH ₂ C(0)
	R4	(2-FPh)CH ₂	PhCH ₂	PhCH ₂	РhСH ₂
	Entry No	118	119	120	121

- 104 -

	PRA CMV EC ₅₀ (µM)	3.3		28	80	. 35
	ELISA CMV EC ₅₀ (µM)		41			
	HSV-1 EC ₅₀ (µM)					
	нsv-1 IC ₅₀ (µМ)		>50		0.159	
TABLE 1 (continued)	FAB/MS (m/z) (MH) ⁺	519	464	476	458	476
	R5	Me SCH ₂ C(O)	Me_N_C(0)	CH ₂ C(O)	(C(O)	(O)2 ⁶ H2 N
	R4	PhCH ₂	PhCH2	(4-FPh)CH ₂	PhCH ₂ CH ₂	(3-FPh)CH ₂
	Entry No	122	123	124	125	126

- 105 -

			TABLE 1 (continued)				
R4 R5	R5		FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀ (µM)	HSV-1 EC ₅₀ (µM)	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
(2-MePh)CH ₂	PS N	,ch ₂ c(0)	472	0.99		8.8	25*
$(2-MePh)CH_2$		~C(0)	463				28
(2-MePh) CH ₂	/	Me OCH ₂ C(O)	515				12
(2-MePh) CH ₂ Me	N N N N N N N N N N N N N N N N N N N	(0)2°H2S_	533				8.8
(2-MePh) CH2 $S CH2$.сн ₂ с(о)	477				16

- 106 -

	a > 9 C			_	_	
	PRA CMV EC ₅₀ (µM)	14	17	18	38	31
	ELISA CMV EC ₅₀ (μM)					
	HSV-1 EC ₅₀ (μΜ)					
	HSV-1 IC ₅₀ (μΜ)			0.26	0.78	4.2
TABLE 1 (continued)	FAB/MS (m/z) (MH) +	477	463	458	472	472
	R5	(O)2 ² H2-CH ² S	s (0)	N C(O)	(0)2 ⁴ H2	(0)2°HO
	R4	(2-MePh) CH ₂	(2-MePh) CH ₂	Ph- (S)-CHMe	Ph∸ (S)-CHMe	Ph- (R)-CHMe
	Entry No	132	133	134	135	136

- 107 -

			TABLE 1				
entry NO	R4	R ⁵	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀ (µM)	HSV-1 EC ₅₀ (µM)	ELISA CMV EC ₅₀	PRA CMV EC50
137	Ph- (R)-CHMe	(C)(O)	458	0.98			49
138	CH ₂	Me-Nc(0)	470	>50		31.6	
139	CH ₂	CH ₂ C(O)	464	0.77			20
140	Me ₂ NCH ₂ CH ₂	(o)o	430	48	9.2	1.4	29
141	Pr ₂ CH	PhCH ₂ OC (0)	481	4	3.5	>121	
142	Me ₃ CCH ₂	Me ₃ COC(0)	419	6.3	2.4	4.0	
143	PhCH ₂	PhCH ₂ NHS(0) ₂	508	8.0	1.0	>64	

Cytotoxic at this concentration

** Includes isotopic peak due to chlorine

_							,		T	т —	<u> </u>
				PRA	EC50	30.	4.7	9.2	>3.7*	8.8*	22
-				ELISA CMV	(MH)	3.2	0.55	1.2	6.6	5.8	1.1
	·			HSV-1 EC ₅₀	(Mn/)	9	2.2	2.2	2.2	2.0	4.8
				HSV-1 IC ₅₀	(Mrl)	21	1.2	2.1	5.2	1.3	5.7
2				FAB/MS (m/z)	(ma)	353	443	457	371	447	458
TABLE	lavi	$\bigvee_{0}^{N}\bigvee_{R_{1}}^{Q}\bigvee_{N}^{N}\bigvee_{R_{5}}$ $NH_{2}, R^{2} \text{ and } R^{3} \text{ each is } H,$	signated as	R ⁵		PhCH ₂	PhCH ₂	Phc (0)	(3-FPh)CH ₂	Phc (0)	(C(0)
	of formula 1			R4		Н	PhCH ₂	PhCH ₂	н	(3-FPh) CH ₂	PhCH ₂
	Compound	$R^{1} \longrightarrow \begin{pmatrix} N \\ S \end{pmatrix}$ wherein R^{1} is	and Q, R follows:	ø		СН ₂	CH ₂	CH ₂	CH ₂	CH ₂	СН2
		医內下氏》	•	Q.		1	2	3	4	5	9

- 109 -

			T			
	PRA CMV EC ₅₀	42	13*	>10.4	14*	20
	ELISA CMV EC ₅₀	7.8	8.6	6.0	7.5	15
	HSV-1 EC ₅₀ (µМ)	3.2	1.1	0.95	3.9	4
	HSV-1 IC ₅₀ (µM)	7.6	1.7	4.0	21	15
2 ed)	FAB/MS (m/z) (MH) ⁺	458	463	379	379	484
TABLE 2 (continued)	R5	N (0)	(o) 2—<	CH CH2 CH2	EP, CF, CF, CF, CF, CF, CF, CF, CF, CF, CF	C(0)
	R4	PhCH ₂	PhCH ₂	н	н	CH ₂ CH ₂
	Ø	CH ₂	СН2	СН2	СН2	CH ₂
	Entry No	7	ω	6	10	11

							T	
	PRA CMV EC ₅₀ (µM)	ω	*	>28	6	*8	^ 5	3.3
	ELISA CMV EC ₅₀ (µM)	6.5	3.7	0.2	11.3	7	4.7	2.9
	HSV-1 EC ₅₀ (μΜ)	7.6	3.4	1.8	0.64	2.6	1.8	1.6
	HSV-1 IC ₅₀ (µМ)	10	2.6	1.7	0.28	1.8	0.76	1.0
2 ed)	FAB/MS (m/z) (MH) ⁺	484	479	479	453	487	449	467
TABLE 2 (continued)	R5	N C (0)	ме ³ сос (о)	Me ₃ COC (0)	Me3COC(0)	(0) 20 ² H244	CH ₂	Ме ₃ СОС (О)
	R4	CH2 CH2 CH2	CH ₂ CH ₂	(H)	PhCH ₂	PhCH ₂	PhCH ₂	Ph- (S) -CHMe
	ō ·	CH ₂	СН2	СН2	CH2	CH_2	CH ₂	СН2
	Entry	12	13	14	15	16	17	18

- 111 -

	T T	T	T	<u> </u>	- 			-	
	PRA CMV EC ₅₀	(HM)	# C	6.5	*9<	*	31	,	14
	ELISA CMV EC ₅₀	(EM)	4.0	4.2	4.8	0 4	0.45	-	0.1
	HSV-1 EC ₅₀ (μM)	0.89	1.3	0.45	9	9	1.7	2	
	HSV-1 IC ₅₀ (µM)	0.46	7.2	0.028	29	45	1.2	13.6	
2	FAB/MS (m/z) (MH) +	457	367	459	359	361	464	367	444
TABLE 2	ጽ	Ph- (S) -CHMe	Ph-(S)-CHMe	Me ₃ COC (O)	CH ₂	Pr2CH	(N)-C(0)	Ph-(R)-CHMe	CH ₂
	R4	РһСН2	Н	$\left\langle \begin{array}{c} \\ \\ \end{array} \right\rangle$	ж	Н	CH ₂	H	PhCH ₂
	ø	CH ₂	СН2	CH ₂	СН2	CH ₂	CH ₂	CH ₂	CH ₂
	Entry No	19	20	21	22	23	24	25	26

- 112 -

					
	PRA CMV EC ₅₀	15		14	13
	ELISA CMV EC ₅₀		18		
·	HSV-1 EC ₅₀ (µM)		2.0		
	HSV-1 IС ₅₀ (µМ)		7.9		
2 ed)	FAB/MS (m/z) (MH) +	450	367	444	459
TABLE 2 (continued)	R ⁵	N-CH ₂ CH ₂	Me	N CH ₂	£ ₹
	R4	PhCH ₂	Ph- (S)-СНМе	PhCH ₂	PhCH ₂
	ō	СН2	CH ₂	СН2	СН2
	Entry No	27	28	29	30

* Cytotoxic at this concentration

- 113 -

Г					T		T
			PRA CMV EC ₅₀	24		80	
			ELISA CMV EC ₅₀	>46	78		12
			HSV-1 EC ₅₀ (µМ)	0.016	0.34	4	0.12
			HSV-1 IC ₅₀ (μM)	0.053	1.5	13	0.19
			FAB/MS (m/z) (MH) +	463	458	353	448
TABLE 3	g the structure	${\rm R}^3$ absent and ${\rm R}^1$, ${\rm R}^2$, ed as follows:	R5	(O) D—C(O)	N	PhCH ₂	C(0)
	formula 1 having the $ \begin{bmatrix} R^2 & & & & & & & & & & & & \\ R^2 & & & & & & & & & & & \\ & & & & & & & &$	D. H. Q is designat	R ⁴	PhCH ₂	PhCH ₂	Н	PhCH ₂
	4 /=	S is R ³ is R ⁵ are	R ²	Же	Me	Me	Ξ
	Compound	R ¹ ——S- Wherein R ⁴ and F	R.1	NH ₂	NH ₂	NH2	Me
		RZHKX	No	н	2	е П	4

- 114 -

		<u> </u>	,	1		1	1	T		Т	
	PRA CMV EC ₅₀ (µM)	16	16					18			
	ELISA CMV EC ₅₀ (µM)	>63	51		9.0	5.0	1.1	3.5	>79	36	
	HSV-1 EC ₅₀ (µM)	0.012	0.012	4.1	0.002	1.3	0.008	0.024	21	>4	
	HSV-1 IC ₅₀ (μΜ)	0.10	0.33	15.0	0.05	10.0	0.31	>50	>50	>50	
	FAB/MS (m/z) (MH) ⁺	434	457	353	463	464	453	471	367	373	
TABLE 3 (continued)	R ⁵	(O) — C(O)	Phc (0)	PhCH ₂	(o)) — c(o)	C(0)	Me ₃ COC (0)	Phc (0)	PhCH ₂		
	R4	PhCH ₂	PhCH ₂	Н	PhCH ₂	CH2	PhCH ₂	PhCH ₂	Н	H	
	R ²	H	н	н	Н	н	н	Н	Н	H	
	R1	н	NHMe	NHMe	NHMe	NHMe	NHMe	NMe ₂	NMe ₂	NMe ₂	
	Entry No	5	9	7	œ	6	10	11	12	13	

- 115 -

				TABLE 3					
Entry No	R1	R ²	R4	(continued)	(MH) +	HSV-1 IC ₅₀ (µМ)	HSV-1 EC ₅₀ (µM)	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
14	име2	н	PhCH ₂	N -C(0)	472	>50	0.5	20	
15	NMe ₂	н	PhCH ₂	C(0)	478	>50	>23	28	
16	NMe ₂	н	PhCH ₂	Me ₃ COC (0)	467	>50	0.009	4.8	
17	NMe ₂	н	$\left\langle \right\rangle$ - $^{\text{CH}_2}$	Me ₃ COC(0)	473	>50	8<	4	
18	Me- C(0)NH	Н	PhCH ₂	CH ³ C (0)	423	>100	>30	2.8	>81
19	Me- C(0)NH	Ħ	PhCH ₂	N	486	>50	6	28	
20	Ме2СН	Ħ	PhCH ₂	Phc (0)	470	>50	>25	3.3	70

- 116 -

_					· · · · · · · · · · · · · · · · · · ·		,
	PRA CMV EC ₅₀ (µM)	1.2	1.3	2.8	3.7	2.7	15
	ELISA CMV EC ₅₀ (μM)						
	HSV-1 EC ₅₀ (µM)						
	HSV-1 IC ₅₀ (µM)						
(continued)	FAB/MS (m/z) (MH) ⁺	619	563	572	558	572	505
TABLE 3 (con	R ⁵	Me SCH ₂ C(O)	(o)5—((O)2 ⁴ CH ₂ C(O)	(C(O)	(O)2 ^c H2 N	(O))—(C(O)
	R4	РћСН ₂	Рћ- (R) -СНМе	Ph- (R)-CHMe	Рћ- <i>(R)</i> -СНМе	Р h- (<i>S</i>) -СНМе	Ph-(R)-CHMe
	R ²	н	Н	н	н	Ħ	н
	R1	Me ₃ CO- C(O)NH	Me ₃ CO- C(O)NH	Me ₃ CO- C(O)NH	Me ₃ CO- C(O)NH	Me ₃ CO- C(O)NH	Ме - С(0) NH
	Entry No	21	22	23	24	25	26

- 117 -

ſ	T		······································				T		
					PRA CMV EC ₅₀	(MH)	,	2 1	1.5
					ELISA CMV EC ₅₀	(MT)			
					HSV-1 EC ₅₀ (µM)				
					HSV-1 IC ₅₀ (μM)				
4					FAB/MS (m/z) (MH) +		543	542	7.5
TABLE	1	A S	z	each is H, Q is CH ₂ are designated as	R ⁵		PhCH ₂	PhCH,	7
	rmula 1 havir	N	= 0	R³ each is H R⁵ are design	R4		PhCH ₂	PhCH ₂	,
	Compound of formula 1 having the structure		R. R. S.	wherein \mathbb{R}^2 and and \mathbb{R}^1 , \mathbb{R}^4 and follows:	R1		Me ₃ COC(0)NH	Me ₃ CNHC(0)NH	
			BZH	¥ >>	No	1.	-	7	

- 118 -

			1500				
			PRA CMV EC ₅₀ (µM)			24	22
			ELISA CMV EC ₅₀ (µM)	14*	52	0.14	0.25
			HSV-1 EC ₅₀	0.079	0.17	0.016	0.57
			HSV-1 IC ₅₀	0.052	0.64	0.046	1.5
2		·	FAB/MS (m/z) (MH) +	449	449	439	439
TABLE	1 having the $ \begin{array}{ccc} R^4 \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ &$	R is H, Q is S are	R ⁵	(0)5-{	(0)5	(о) 202 ⁸ ем	Me3COC (0)
	formula 1)	$^{\circ}$	R ⁴	н	н	н	н
	Compound of for structure	$R^1 \longrightarrow R^1$ wherein R^1 is a absent and R^3 , designated as f	Ŗ ³	(S)-PhcH ₂	(R)-PhCH ₂	(S)-PhCH ₂	(R)-PhCH ₂
		医对中氏炎	No	1	2	3	4

- 119 -

	45.0		T		T		\top		_	T	
	PRA CMV EC ₅₀	(EM)	ı	-	33	8.7	12	8			
	ELISA CMV EC ₅₀	9.5	0 14	6<	1.1	4.0	2.5	1.4	4.1	14	10
	HSV-1 EC ₅₀	(µm) 0.15	0.83	2.1	14	0.29	0.059	0.51	0.82	2.0	0.009
	HSV-1 IC ₅₀	0.22	1.06	9.9	45	0.052	0.090	0.40	1.3	2.0	0.11
M S	FAB/MS (m/z) (MH) +	463	429	429	353	539	453	539	353	353	463
TABLE 5	R ⁵	(O)2—C	PhCH ₂	PhCH ₂	Me		Me ₃ COC (0)	(0)5—C(0)	PhCH ₂	PhCH ₂	(0)5-
	R4	Me	Н	Н	н	PhcH ₂	Me	PhCH ₂	H	H	PhCH ₂
	R ³	(S)-PhCH ₂	(S)-PhCH ₂	(R)-PhCH ₂	(S)-PhCH ₂	(R)-PhCH ₂	(S)-PhCH ₂	(S)-PhCH ₂	(S)-Me	(R)-Me	(S) -Me
	Entry No	2	9	7	ω (ע	10	11	12	13	14

- 120 -

TABLE 5 (continued)	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	(R)-Me PhCH ₂ $\langle -C(0) \rangle$ 463 0.041 0.006 3.2	(S)-Me PhCH ₂ Me ₃ COC(O) 453 0.46 0.079 2.8	(R)-Me PhCH ₂ Me ₃ COC(0) 453 0.11 0.055 7.6	(R)-PhCH ₂ H Me 353 24.5 >48	(S)-PhCH ₂ H Me ₃ CCH ₂ C(O) 437 0.051 0.040 3.8 21*	(S)-PhCH ₂ H Me ₃ CC(0) 423 1.3 0.60 10	(S)-PhCH ₂ H MeC(O) 381 3.1 4.7 4.4	(S)-PhCH ₂ H Me ₂ CHOC(O) 425 0.83 0.25 18	(S)-PhCH ₂ H PhCH ₂ OC(0) 473 0.60 0.094	$\left\langle \begin{array}{c ccc} & H & Me_3COC(0) & 445 & 0.017 & 0.043 & 8.1 \\ \hline \\ & & & \\ \end{array} \right\rangle$	
		(R)-Me	(S)-Me	(R)-Me	(R)-PhCH ₂	(S) - PhCH ₂	(S) - PhCH ₂	(S) - PhCH ₂	(S)-PhCH ₂	(S)-PhCH ₂	$(S) \bigcirc $]
	Entry No	15	16	17	18	19	20	21	22	23	24	

- 121 -

R3 (S) - PhCH	R ⁴ Н	TABLE (contin	E 5 nued) FAB/MS (m/z) (MH) + 488	HSV-1 IC ₅₀ (µМ) 0.17	HSV-1 EC ₅₀ (µM) 0.10	ELISA CMV EC ₅₀ (μΜ) 0.6	PRA CMV EC ₅₀ (µM) 55
		R3 (S)-PhCH2	R3 R4 R5 $(S) - PhCH_2 H O N-S$ $(S) - PhCH_2 H O N-S$	(continue) R3 R4 R5 (S)-PhCH2 H ON-S(O)2 (C)2 (C)2 (C)3 (C)3 (C)4 (C)4 (C)4 (C)5 (C)5 (C)5 (C)6 (C)6 (C)6 (C)6 (C)7 (C)7 (C)7 (C)7 (C)7 (C)7 (C)7 (C)7	R3 R4 R5 (m/z) $(MH)^+$ (S) $-PhCH_2$ H O $N-S(O)_2$ 488	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$

Cytotoxic at this concentration

- 122 -

NH			-		LB 6				
We and R ⁵ are designated as wand R ⁵ are designated as uration* (m/z) $($	= =	ot J	н ,	ring the					
and K ⁵ are designated as R ⁵ Config- uration* PhCH ₂ RAB/MS (m/z)	1 3								
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	16 G	≊		1					
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	-	3	R.5	Config- uration*	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀	HSV-1 EC ₅₀	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
PhCH2 S 393 6.2 2.6 22 Me3COC (0) S 399 6.2 2.1 1.4 PhC (0) S 0.46 0.21 >64 PhC (0) S 393 1.6 0.17 63 $\langle \rangle_{-C(0)}$ S 399 0.052 0.016 28	Ü	(0)	PhcH ₂	R	393	12	3.4	0.25	80
	Ü	(0)	PhCH ₂	S	393	6.2	2.6	22	50
Me ₃ COC(0) S 0.46 0.21 >64 PhC(0) S 393 1.6 0.17 63 $\langle - \rangle_{-C(0)}$ S 399 0.052 0.016 28	ົວ	(0)	CH2	ĸ	399	6.2	2.1	1.4	45
Phc(0) S 393 1.6 0.17 63 \bigcirc \bigcirc C(0) \bigcirc S 399 0.052 0.016 28	ן ט	H ₂	Me3COC(0)	S		0.46	0.21	>64	
S 399 0.052 0.016 28	ان	H ₂	Phc (0)	\mathcal{S}	393	1.6	0.17	63	>89
	ບ	H2	(o) D—C(o)	S	399	0.052	0.016	28	22

- 123 -

			TAB	TABLE 6				
Entry)				
Ž,		•		FAB/MS	HSV-1	HSV-1	ELISA	PRA
2	3	c ^R	Config-	(m/z)	IC ₅₀	EC50	EC ₅₀	EC ₅₀
T			utacton	(um)	(MId)	(MII)	(IIM)	(MI)
7	CH ₂	PhCH ₂	S	379	1.5	1.1	>3.3	
α	200	10,000						
0	ر دىء	MegCOC(0)	R	389	7.5	1.8	11	>83
6	CH ₂	Phc (0)	R	393	1.6	0.59	0.30	00/
10	CH2		R	399	0.13	0.025	0.60	900
						i) †

Configuration of the asymmetric carbon atom linked to the $-(\mathrm{CH}_2)_2 \mathtt{W}^-$ group

5

In addition to the above results, certain Group 1 compounds have been tested against cutaneous HSV-1 infection in the SKH-1 hairless mouse model (P.H. Lee et al., supra). In this instance, viral pathology was monitored using a subjective scoring system and infection was initiated by spreading a viral inoculum (HSV-1 KOS, 7.3 X 10⁷ PFU) over punctured skin. Following suspension/dissolution of the test compound in 0.03 N aqueous HCl, oral administration for five days tid, commencing three hours post infection, resulted in a significant reduction of viral pathology for the Group 1 compounds from TABLE 1 as follows:

15

20

25

10

TABLE 1	ED ₅₀ (mg/kg/day)				
Entry No.					
58	31				
36	51				
29	56				
49	129				

Antiviral activity for Group 1 compounds was also observed in the mouse genital model of R.W. Sidwell et al., supra. Vaginal HSV-2 infection in the Swiss Webster mouse was initiated by vaginal irritation and instillation of HSV-2 (HSV-2 HG-52, 1 x 10^7 PFU). Viral pathology was measured as described above. Following oral administration in the above vehicle, and commencing three hours post infection, the following reductions in viral pathology were observed for the Group 1 compounds in TABLE 1: Entry 29 produced a dose-dependent (ED₅₀ = 60

- 125 -

mg/kg/day) reduction of viral pathology and Entry 28 at 100 mg/kg/day produced a 30% reduction of viral pathology.

Furthermore, certain Group 1 compounds have been 5 subjected to cutaneous testing. The compounds were formulated as a 3% (w/w) composition in an emulsion cream having the following composition: Pegoxal 7 Stearate® (a mixture of different molecular weight steric acid esters of polyethylene glycol) 14%; 10 Peglicol 5 Oleate ® (glycosylated glycerides) 3%; light mineral oil 2%; Transcutol ® (diethoxy glycol) 10%; parabens (a mixture of methyl and propyl esters of 4-hydroxybenzoic acid) 0.15%; and 15 deionized water qs to 100%). Cutaneously HSV-1 infected hairless mice (see above for protocol) were treated qid beginning 3 h post inoculation for five days by liberally applying the cream over the inoculation area. Evidence of disease was scored as 20 described above. The following results were obtained.

Compound (3% w/w Cream)	% Reduction of Cutaneous Pathology
Entry No. 1	95
Entry No. 28	79
Entry No. 24	88
Entry No. 29	95
Entry No. 29	23
(Treatment 24 h post	1
inoculation)	

In addition the dose-dependence of Entry No. 29 following topical application to the skin was evaluated and the ED₅₀ was found to be 0.1 % w/w.

Still furthermore, oral doses of Entry No. 29 of Group 1 at 50 mg/kg/day and 100 mg/kg/day were active in the preceding mouse model when treatment was initiated at 65 h post inoculation. Also, topical treatment of cutaneous HSV-2 infections, namely HG-52 or the acyclovir resistant HSV-2 strain VK-1 (C.S. Crumpacker, New Engl. J. Med., 1989, 320, 293) infections, in the mouse model with the above noted 3% w/w formulation of Entry No. 29 was therapeutically effective, producing a 58 to 72% reduction of viral pathology.

The therapeutic effectiveness of the compounds of Group 1 for treating acyclovir-resistant herpes infections in a mammal can be demonstrated by testing the compounds in an immunodeficient animal model (female nu/nu mice, 5-6 weeks old). were cutaneously inoculated with 107 PFU of HSV-1 acyclovir resistant mutant viruses. The resulting cutaneous lesions were scored according to a subjective scoring system. The compound of Group 1 (Entry No. 29 in table 1) was administered orally (gavage) in an acidified vehicle (0.033 N aqueous HCl, tid for 10 days). Animals were similarly treated with acyclovir in 0.033 N aqueous HCl or only with the vehicle (0.033 N aqueous HCl). animals infected with the HSV-1 acyclovir-resistant mutant strain PAAr5, Entry No. 29 dose-despondently reduced cutaneous lesions (Figures 1 and 2). cutaneous lesions were almost abolished by treatment

- 127 -

20

25

30

with Entry No. 29 at a dose of 100 mg/kg/day $(-\triangle-)$, while acyclovir at the same dose $(-\phi-)$, or vehicle alone (-O-), had no effect on cutaneous lesions (Figure 1). The dose-dependent effect of treatment with Entry No. 29 at 25 mg/kg/day $(-\phi-)$, 5 $mg/kg/day (-\Delta-)$, 75 mg/kg/day (-D-), 100 mg/kg/day $(-\bullet-)$ or 125 mg/kg/day $(-\blacksquare-)$, compared to treatment with vehicle alone (-O-), is shown in Figure 2. The ED_{50} of Entry No. 29 was about 60 mg/kg/day. Similar experiments were done using the HSV-1 10 acyclovir-resistant mutant strain dlsptk (Figures 3 and 4). In this case the cutaneous lesions were again almost abolished by treatment with Entry No. 29 at a dose of 100 mg/kg/day (- \triangle -), while acyclovir at the same dose $(-\phi-)$, or vehicle alone 15 (-O-), had no effect on cutaneous lesions (Figure 3). The dose-dependent effect of treatment with Entry No. 29 at 25 mg/kg/day $(-\phi-)$, 50 mg/kg/day $(-\Delta-)$, 75 mg/kg/day $(-\Box-)$, 100 mg/kg/day $(-\bullet-)$ or 20 125 mg/kg/day (-m-), compared to treatment with vehicle alone (-O-), is shown in Figure 4.

The acyclovir-resistant HSV-1 strains, PAAr5 and dlsptk, have been described by P.A. Furman et al.,

J. Virol., 1981, 40, 936 and by D.M. Coen et al.,

Proc. Natl. Acad. Sci., 1989, 86, 4736,
respectively.

Group 2: N-(Thiazolylphenyl)ureido Derivatives

According to another embodiment of this invention, the present application refers to Group 2-N-

(thiazolylphenyl)ureido derivatives having antiherpes activity. The selective action of these compounds against these viruses, combined with a wide margin of safety, renders the compounds desirable agents for combating herpes infections.

10

15

The N-(thiazolylphenyl)ureido derivatives of the present invention can be characterized structurally by the presence of N-{4-(4-thiazolyl)phenyl}ureido moiety. Compounds possessing such a moiety have been reported previously, for example:

K.D. Hargrave et al., J. Med. Chem., 1983, 26,
1158:

C.G. Caldwell et al., US patent 4,746,669,
issued May 24, 1988;

- A. Wissner, European patent application
 458,037, published November 27, 1991; and
 A. Leonardi et al., PCT patent application WO
 95/04049, published February 9, 1995.
- The present N-(thiazolylphenyl)ureido derivatives can be distinguished readily from the prior art compounds in that they possess different chemical structures and biological activities.
- 30 The Group 2 N-(thiazolylphenyl)ureido derivatives of this invention can also be represented by formula la:

- 129 -

$$\begin{array}{c|c}
R^{1A} & N \\
N & N \\
N & R^{4A}
\end{array}$$
(1a)

wherein R^{1A} has the same meaning as R as defined hereinbefore and R^{2A} , A, R^{3A} and R^{4A} are as defined hereinbefore.

5

A preferred set of Group 2 compounds of this invention is represented by Group 2-formula 1a wherein R^{1A} is selected from the group consisting of hydrogen, lower alkyl, amino, lower alkylamino,

- di(lower alkyl)amino, lower alkanoylamino, (lower alkoxycarbonyl)amino, ((lower alkylamino)carbonyl)amino and 2-, 3- or 4-pyridinylamino; R^{2A} is hydrogen, methyl or ethyl; A is absent or carbonyl; R^{3A} is hydrogen, (1-8C)alkyl,
- 2-hydroxyethyl, 3-hydroxypropyl, (1-3C)alkyl monosubstituted with cyano, phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted or disubstituted on the aromatic portion thereof with halo, hydroxy, di(lower alkyl)amino, lower alkoxy or lower alkyl;
- 20 (lower cycloalkyl)-(lower alkyl) or (Het)-(lower alkyl) wherein Het is as defined hereinbefore; and R^{4A} is (1-8C)alkyl, phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted or disubstituted on the aromatic portion thereof with halo, hydroxy,
- di(lower alkyl)amino, lower alkoxy or lower alkyl;
 1-indanyl, 2-indanyl, 1-(hydroxymethyl)-2phenylethyl, (lower cycloalkyl)-(1-3C)alkyl, Het as
 defined hereinbefore, (Het)-(1-3C)alkyl wherein Het
 is as defined hereinbefore or 3-1H-indolylethyl; or
 R^{4A} is:

wherein L is oxygen or nitrogen, with the proviso that when L is oxygen, one of R^{6A} or R^{7A} is absent; R^{5A} and R^{6A} are independently selected from the group defined for R3A herein; and R7A is independently selected from the group defined for R^{4A} herein; or R^{3A} and R^{4A} together with the nitrogen to which they are attached form an unsubstituted, 10 monosubstituted or disubstituted five or six membered, monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently from the group consisting of 15 halo, hydroxy, lower alkoxy and lower alkyl; or a therapeutically acceptable acid addition salt thereof.

A more preferred set of Group 2 compounds are 20 represented by Group 2-formula la wherein R1A is hydrogen, amino, methyl, methylamino, butylamino, dimethylamino, acetylamino, (1,1dimethylethoxycarbonyl)amino, 2-pyridinylamino or 3pyridinylamino; R2A is hydrogen or methyl; A is 25 absent or carbonyl; R3A is hydrogen, methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-propylbutyl, 2-hydroxyethyl, cyanomethyl, phenylmethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4fluorophenyl)methyl, {4-(dimethylamino)phenyl}-30 methyl, (4-methoxyphenyl)methyl, (2-methyl-

- 131 -

ph (1) methyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclohexylethyl, 2-(4-morpholinyl)ethyl, 2pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl or 3-thienyl-5 methyl; and R^{4A} is 1,1-dimethylethyl, butyl, 2,2dimethylpropyl, 1-propylbutyl, phenylmethyl, 1(R)phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, (4chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-10 fluorophenyl) methyl, (4-fluorophenyl) methyl, 4-(methoxyphenyl)methyl, {4-(dimethylamino)phenyl}methyl, (2-methylphenyl)methyl, 1-indanyl, 2indanyl, (S or R) - 1 - (hydroxymethyl) - 2 - phenylethyl, cyclopentylmethyl, cyclohexylmethyl, 1(S)-15 cyclohexylethyl, 1(R)-cyclohexylethyl, 2cyclohexylethyl, 1-piperidinyl, 2-(4morpholinyl)ethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-20 thienylmethyl, 3-(1H-imidazol-1-yl)propyl or 3-1Hindolylethyl; or R^{4A} is:

wherein L oxygen or nitrogen, with the proviso that
when L is oxygen, one of R^{6A} or R^{7A} is absent; R^{5A}
and R^{6A} are independently selected from the group
defined for R^{3A} herein; and R^{7A} is independently
selected from the group defined for R^{4A} herein; or
R^{3A} and R^{4A} together with the nitrogen atom to which
they are attached form a pyrrolidino, piperidino,

morpholino or thiomorpholino; or a therapeutically acceptable acid addition salt thereof.

A most preferred set of Group 2 compounds are

represented by Group 2-formula 1a wherein R^{1A} is
amino, methylamino, dimethylamino or (1,1dimethylethoxycarbonyl)amino; R^{2A} is hydrogen; A is
absent; R^{3A} is hydrogen, methyl or butyl; and R^{4A} is
1,1-dimethylethyl, butyl, 1-propylbutyl, phenylmethyl, 2-phenylethyl, 4-fluorophenylmethyl, 1piperidinyl, 2-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 4-pyridinylmethyl, 3-(1H-imidazol-1-yl)propyl, or
R^{4A} is:

15

20

25

30

wherein L is nitrogen, R^{5A} is phenylmethyl, R^{6A} is methyl and R^{7A} is 2-(2-pyridinyl)ethyl, or L is oxygen, R^{5A} is phenylmethyl, R^{6A} is absent and R^{7A} is 1,1-dimethylethyl; or a therapeutically acceptable acid addition salt thereof.

Another most preferred set of Group 2 compounds are represented by Group 2-formula 1a wherein R^{1A} is amino, methylamino, butylamino, dimethylamino, (1,1-dimethylethoxycarbonyl)amino, 2-pyridinylamino or 3-pyridinylamino; R^{2A} is hydrogen; A is absent; R^{3A} is hydrogen, methyl, ethyl, butyl, 2-hydroxyethyl, cyanomethyl or phenylmethyl; and R^{4A} is butyl, phenylmethyl or 2-(4-pyridinyl)ethyl; or a therapeutically acceptable acid addition salt therof.

- 133 -

Still another most preferred set of Group 2 compounds are represented by Group 2-formula 1a wherein R^{1A} is amino, R^{2A} is hydrogen, A is carbonyl, R^{3A} is butyl or phenylmethyl, and R^{4A} is butyl or phenylmethyl, or a therapeutically acceptable acid addition salt therof.

Included within the scope of this invention is a pharmaceutical composition comprising an antiherpes virally effective amount of a compound of Group 2 as defined herein, or a therapeutically acceptable acid addition salt thereof, and a pharmaceutically or veterinarily acceptable carrier.

15 Still another aspect of this invention involves a method for treating acyclovir-resistant herpes infections in a mammal which comprises administering to the mammal an anti-acyclovir-resistant herpes effective amount of a compound of Group 2 as defined 20 herein, or a therapeutically acceptable acid addition salt thereof.

Process for Preparing the Compounds of Group 2

The compounds of Group 2 can be prepared by a variety of processes. Description of such methods are found in standard textbooks such as "Annual Reports In Organic Synthesis - 1994", P.M. Weintraub et al., Eds., Academic Press, Inc., San Diego, CA, USA, 1994 (and the preceding annual reports), "Vogel's Textbook of Practical Organic Chemistry", B.S. Furniss et al., Eds., Longman Group Limited, Essex, UK, 1986, and "Comprehensive Organic

Synthesis", B.M. Trost and I. Fleming, Eds., Pergamon Press, Oxford, UK, 1991, Volumes 1 to 8.

Generally speaking, the compounds of Group 2-formula

1 a can be prepared by a process selected from the
following processes (a), (b), (c) or (d):

(a) reacting in the presence of N, N'-carbonyldiimidazole a compound of the formula:

10

15

wherein R^{1AA} is hydrogen, lower alkyl, (amino protecting group)-amino, (amino protecting group)-(lower alkylamino) or di(loweralkyl)amino and R^{2A} is hydrogen or lower alkyl, with an amine of the formula:

$$HN < R^{3A}$$

wherein R^{3A} and R^{4A} are as defined herein, followed by, if required, removing any N-protecting groups and effecting standard transformations, to obtain the corresponding compound of Group 2-formula 1a wherein A is absent and R^{1A}, R^{2A}, R^{3A} and R^{4A} are as defined herein;

(b) reacting an isocyanate of the formula:

25

- 135 -

with an amine of the formula:

wherein R^{3A} and R^{4A} are as defined herein, to obtain the corresponding ureido derivative of the formula:

5

and either (i) reacting the latter ureido derivative with a thiourea derivative of the formula $H_2N-C(S)$ - R^{1BB} wherein R^{1BB} is amino, lower alkylamino or di(lower alkyl)amino, and a halogen, selected from Br_2 , Cl_2 or I_2 , to obtain the corresponding compound 10 of formula la wherein RlA is amino, lower alkylamino or di(lower alkyl)amino, R2A is hydrogen, A is absent and R^{3A} and R^{4A} are as defined herein; or (ii) reacting the latter wreido derivative with Br2, Cl_2 or I_2 whereby the methyl ketone moiety of the 15 ureido derivative is converted to a haloketone moiety to give the corresponding α -haloketone and reacting the α -haloketone with a thioamide of the formula $H_2N-C(S)-R^{1CC}$ wherein R^{1CC} is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)-20 amino to obtain the corresponding compound of formula la wherein RlA is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl) amino, R^{2A} is hydrogen, A is absent and R^{3A} and R^{4A} are as defined herein; and, if required, eliminating from 25 the instant product of (i) or (ii) any protective groups, and effecting standard transformations to obtain the corresponding compound of Group 2-formula

la wherein A is absent, R^{1A} , R^{3A} and R^{4A} are as defined herein and R^{2A} is hydrogen;

(c) reacting a compound of the formula:

5

with an amine of the formula:

10

wherein R^{3A} and R^{4A} are as defined herein, to obtain the corresponding compound of formula la wherein R^{1A} is amino, R^{2A} is hydrogen, and R^{3A} and R^{4A} are as defined herein;

15

(d) reacting a compound of the formula:

wherein \mathbb{R}^{1A} and \mathbb{R}^{2A} are as defined herein (prepared 20 as described in the following Group 2-schemes 1 and 2), with a reagent of the formula:

- 137 -

wherein R^{3A} and R^{4A} are as defined herein, to obtain the corresponding compound of Group 2-formula 1a 5 wherein A is carbonyl, and R^{1A}, R^{2A}, R^{3A} and R^{4A} are as defined herein. The above reagent is prepared by reacting an equivalent amount of oxalyl chloride and the corresponding amine of the formula:

$$HN < R^{3A}$$

10

in the presence of a tertiary organic amine, for example diisopropylethylamine.

More explicitly, a practical and convenient procedure to prepare compounds of Group 2-formula la is illustrated by Group 2-scheme 1:

Group 2 - Scheme 1

According to Group 2-scheme 1, the amino substituent of 4'-aminoacetophenone (2) is protected with a known amino protecting group PG₁ (for example 2,2,2-trichloroethoxycarbonyl, (phenylmethoxy)carbonyl, tert-butoxycarbonyl, {(4-methoxyphenyl)methoxy}-carbonyl or the like) to yield the amino protected compound of formula 3. The terminal methyl ketone moiety of the compound of formula 3 is converted to a 2-aminothiazolyl moiety by reaction with thiourea and iodine according to the method of R.M. Dodson and L.C. King, J. Amer. Chem Soc. 1945, 67, 2242 to give the corresponding aminothiazole derivative of formula 4. The 2-amino moiety of the 2-aminothiazolyl moiety is then protected with an amino

(7)

(6)

- 139 -

SUBSTITUTE SHEET (RULE 26)

5

10

protecting group PG_2 to give the compound of formula 5. The amino protecting groups PG_1 and PG_2 are selected such that one of the groups can be selectively removed while leaving the other group intact. The amino protecting group PG_1 is then removed under conditions that do not affect the amino protecting group PG2 to give the compound of formula 6. The compound of formula 6 is converted to the ureido derivative of formula 8 by reaction with N, N'-carbonyldiimidazole and an amine of formula 7 wherein R^{3A} and R^{4A} are as defined herein. In the instance where $NH-PG_2$ has the same significance as R^{1A} as defined herein, then the compound of formula 8 is also compound of formula 1a. Alternatively, the compound of formula 8 can be 15 deprotected to give the corresponding compound of formula 1a wherein R^{1A} is amino. This latter product, albeit a compound of Group 2-formula 1a, can also serve as an intermediate for further elaboration by standard methods to yield other 20 compounds of Group 2-formula 1a.

Another general procedure for preparing compounds of Group 2-formula 1a can be represented by Group 2-scheme 2:

Group 2 - Scheme 2

According to Group 2-scheme 2, 2-bromo-4'nitroacetophenone of formula 2A is reacted with the
appropriate thioamide of formula $H_2N-C(S)-R^{1CC}$ wherein R^{1CC} is hydrogen, lower alkyl, amino, lower
alkylamino or di(lower alkyl amino) to give the
corresponding nitro derivative of formula 9. The
nitro derivative of formula 9 is reduced with iron
and hydrochloric acid to give the thiazolyl
derivative of formula 10. The compound of formula
10 is converted to the ureido derivative of formula
11 by reaction with N,N'-carbonyldiimidazole and an
amine of formula 7 wherein R^{3A} and R^{4A} are as
defined herein. The ureido derivative of formula

- 141 -

SUBSTITUTE SHEET (RULE 26)

10

11, which is also a compound of Group 2-formula 1a, can also serve as an intermediate for further elaboration by standard methods to yield other compounds of Group 2-formula 1a.

5

Another general procedure for preparing compounds of Group 2-formula 1a can be represented by Group 2-scheme 3:

Group 2 - Scheme 3

10 According to Group 2-scheme 3, the classical method for preparing a urea (see, for example, P.A.S. Smith, Organic Reactions, 1946, 3, 376-377) is applied by reacting directly a free N-terminal derivative of formula 7, wherein R^{3A} and R^{4A} are as defined herein, with 4-acetylphenyl isocyanate (12) to yield the ureido derivative of formula 13. The terminal ketone moiety of the ureido derivative of formula 13 is converted to a thiazolyl moiety by first reacting the ureido derivative 13 with Br₂,

(13)

 Cl_2 or I_2 to give the corresponding α -haloketone and reacting the α -haloketone with the appropriate thioamide as described before to give the corresponding thiazole derivative of formula 14 wherein R1CC is as defined herein, which is also a compound of Group 2-formula 1a. Alternatively, the ureido derivative of formula 13 can be directly converted to the thiazolyl derivative of formula 14 wherein R1CC is amino, lower alkylamino or di(lower alkyl) amino by heating the ureido derivative of 10 formula 13 with an appropriate thiourea derivative of the formula $H_2N-C(S)-R^{1CC}$, wherein R^{1CC} is amino, lower alkylamino or di(lower alkyl)amino, in the presence of Br2, Cl2 or I2 according to the classical methods of R.M. Dodson and L.C. King, J. Amer. Chem. Soc. 1945, 67, 2242.

The compound of formula 14 can also serve as an intermediate for further elaboration by standard 20 methods to yield other compounds of Group 2-formula la.

Another general procedure for preparing compounds of Group 2-formula 1a can be represented by Group 2-scheme 4:

30

- 143 -

Group 2 - Scheme 4

According to Group 2-scheme 4, the free amino moiety of 4'-aminoacetophenone (2) is converted to the carbamate derivative of formula 15 by reation with isobutyl chloroformate. The terminal methyl ketone moiety of the carbamate derivative of formula 15 is converted to 2-aminothiazolyl by reaction with thiourea and iodine according to the method of R.M. Dodson and L.C. King, J. Amer. Chem. Soc. 1945, 67, 2242 to give the corresponding aminothiazole

- 144 -

derivative of formula 16. The aminothiazole derivative of formula 16 is reacted with an amine of formula 7, wherein R^{3A} and R^{4A} are as defined herein, to give the ureido derivative of formula 17, which is also a compound of formula 1a. The compound of formula 17 can also serve as an intermediate for further elaboration by standard methods to yield other compounds of Group 2-formula 1a.

10

15

Starting materials for the preceding processes are known or can be readily prepared from known starting materials. 4'-Aminoacetophenone (2) of Group 2-schemes 1 and 4 is available from the Aldrich Chemical Co., Milwaukee, WI, USA. 2-Bromo-4'-nitroacetophenone also is available from the Aldrich Chemical Co. 4-Acetylphenyl isocyanate (12) of Group 2-scheme 3 is available from Lancaster

Synthesis Inc., Windham, NH, USA.

20

25

30

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, the reaction can be successfully performed by conventional modification known to those skilled in the art, e.g. by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, or by modification illustrated in the examples herein.

- 145 -

Furthermore, if desired, the compound of Group 2formula la can be obtained in the form of a
therapeutically acceptable acid addition salt. Such
salts can be considered as biological equivalent of
the compounds of Group 2-formula la. Examples of
such salts are those formed with hydrochloric acid,
sulfuric acid, phosphoric acid, formic acid, acetic
acid or citric acid.

10 Antiherpes Activity

5

25

30

The antiviral activity of the compounds of Group 2formula 1a, or their corresponding therapeutically
acceptable acid addition salts, can be demonstrated
in the same manner as described hereinbefore for the
compounds of Group 1-formula 1. Likewise, the
compounds of Group 2-formula 1a, or their
corresponding therapeutically acceptable acid
addition salts, can be formulated and employed as
antiviral agents in the same manner as described
hereinbefore for the compounds of Group 1-formula 1.

The following examples (Group 2 examples) further illustrate this invention. Temperatures are given in degrees Celsius. Solution percentages or ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance spectra were recorded on a Bruker 400 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. The concentrations for the optical rotations are expressed in grams of the compound per 100 mL of solution. Abbreviations or symbols used in the examples are as defined hereinbefore.

GROUP 2 EXAMPLES

Example 1

- 5 N'-{4-(2-Amino-4-thiazolyl)phenyl}-N-methyl-N-{2-(2-pyridinyl)ethyl}urea (1a: R^{1A}=NH₂, R^{2A}=H, A is absent, R^{3A}=methyl and R^{4A}=2-pyridinylethyl)
- (a) 2,2,2-Trichloroethyl N-{4-(2-amino-4-thiazolyl)-10 phenyl}carbamate: 2,2,2-Trichloroethyl chloroformate (72.3 mL, 0.52 mol) was added (5 min) to an ice cold suspension of 4'-aminoacetophenone (67.6 g, 0.50 mol) and pyridine (50.5 mL, 0.62 mol) in CH₂Cl₂ (1 L). The reaction mixture was stirred at 0° for 15 minutes and then at room temperature (20-22°) for 45
- min. The solvent was removed under reduced pressure. Et₂O (500 mL) and 1N aqueous HCl (500 mL) were added to the residue. The resulting solid was collected by filtration, washed with H₂O (1 L) and
- 20 Et₂O (1 L) and dried over P₂O₅ in a desiccator under reduced pressure for 15 h to yield the expected carbamate (137.8 g, 89% yield). A mixture of the crude carbamate (137.8g, 0.44 mol), thiourea (135.0 g, 1.77 mol) and I₂ (202.6 g, 0.80 mol) in
- isopropanol (670 mL) was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and EtOAc (1 L) was added. The solution was washed serially with $\rm H_2O$ (2 x 600 mL), saturated aqueous NaHCO₃ (2 x 1 L) and $\rm H_2O$ (2 x 1 L). A mixture of
- 30 the organic layer and 4N aqueous HCl (750 mL) was stirred vigorously at room temperature for 1.5 h. Et₂O (~800 mL) and H₂O (~300 mL) were added to the mixture to facilitate stirring. The suspension was filtered and the solid was washed with a 1:1 mixture

- 147 -

of EtOAc and Et₂O (2 L). The solid was suspended in 20% aqueous NaOH (1.2 L) and the mixture was extracted with EtOAc (2 L). The EtOAc extract was washed with brine (700 mL), dried (MgSO₄), and concentrated under reduced pressure to yield 2,2,2-trichloroethyl N-{4-(2-amino-4-thiazolyl)phenyl}-carbamate (117.7 g, 75% yield) as a pale yellow solid: 1 H NMR (400 MHz, DMSO-d₆) δ 10.18 (s,1H), 7.74 (d,J=8.6 Hz, 2H), 7.51 (d,J-8.6 Hz, 2H), 7.01 (s, 2H) 6.88 (s, 1H), 4.95 (s, 2H); MS (FAB) m/z 366/368/370/372 (MH)+.

(b) tert-Butyl N-{4-(4-Aminophenyl)-2-thiazolyl}carbamate: A solution of (Boc)₂O (87.7 g, 0.40 mol) in CH_2Cl_2 (85 mL) and DMAP (4.08 g, 33.0 mmol) was 15 added (10 min) to a cooled (0°) solution of the product of the preceding section a) (117.7g, 0.33 mol) and pyridine (135.0 mL, 1.67 mol) in THF (500 mL) and $\mathrm{CH_2Cl_2}$ (1 L). The reaction mixture was stirred at room temperature for 15 h. 20 The reaction mixture was diluted with EtOAc (1.5 L) and Et_2O (1 L). The resulting solution was washed serially with ${
m H_2O}$ (1 L), 10% (w/v) aqueous citric acid (2 x 500 mL), 1N aqueous HCl (500 mL), $\mathrm{H}_{2}\mathrm{O}$, saturated aqueous 25 $NaHCO_3$ (2x 1L) and brine (1 L), dried (MgSO₄) and concentrated under reduced pressure to give a pale yellow foam (163 g). The latter foam (160 g, 0.34mol) was diluted in 1,4-dioxane (1.72 L) and the solution cooled to 10°. Zn powder (224 g, 3.43 mol) and 1N aqueous HC1 (3.4 L) was added to the cooled 30 solution. The reaction mixture was mechanically stirred at room temperature for 1.5 h. suspension was filtered and the collected material was washed with 1N aqueous HCl (~1 L). Aqueous 20%

- NaOH (2 L) was added to the filtrate (including the acidic wash). The resulting mixture was extracted with EtOAc (9 L total). The EtOAc extract was filtered through diatomaceous earth. The filtrate was washed with brine, dried (MgSO₄) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2 , EtOAc: Hex, 1:2 to 2:3) of the residue gave tert-butyl N-{4-(4aminophenyl)-2-thiazolyl)carbamate (48.3 g, 43% yield) as a pale yellow foam: ^{1}H NMR (400 MHz, DMSO-10 d_6) δ 11.40 (s, 1H), 7.52 (d, J=7.2 Hz, 2H), 7.12 (s, 1H), 6.57 (d, J=7.2 Hz, 2H), 5.20 (s, 2H), 1.48 (s, 9H); MS (FAB) m/z 292 (MH)+.
- 15 (c) The title compound: 1,1'-Carbonyldiimidazole (1.82 g, 11.3 mmol) was added to a solution of the product of the preceding section (b) (3.00 g, 10.3 mmol) in THF (50 mL) at room temperature. reaction mixture was stirred at room temperature for 1.5 h, 2-{2-(methylamino)ethyl}pyridine (2.85 mL, 20 20.6 mmol) was added and the mixture was stirred for another 2 h. EtOAc (500 mL) was added and the resulting solution was washed serially with H2O (100 mL), saturated aqueous NaHCO $_3$ (2 x 100 mL) and brine (100 mL), then dried (MgSO $_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂, EtOAc:MeOH, 12:1) to give the Boc derivative of the title compound which was treated with trifluoroacetic acid (20 mL) in CH_2Cl_2 (40 mL) at room temperature for 3 h. 30 The solution was concentrated under reduced pressure. residue was taken up in EtOAc (300 mL) and the solution washed with 1N aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL).

- 149 - .

combined organic layers were washed with H₂O, dried
 (MgSO₄) and concentrated under reduced pressure.
Purification by flash chromatography (SiO₂,
 CH₂Cl₂:MeOH, 15:1) and recrystallisation (EtOAc:Hex)

5 gave the title compound (0.45 g, 12% yield) as white
 crystals: ¹H NMR (400 MHz, DMSO-d₆) δ 8.52 (d, J =
 4.5 Hz, 1H), 8.39 (s, 1H), 7.71 (~ddd, J = 7.8, 7.5,
 1.8 Hz, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.44 (d, J =
 8.7 Hz, 2H), 7.31 (d, J = 7.8 Hz, 1H), 7.22 (broad

10 dd, J = 7.5, 4.5 Hz, 1H), 6.96 (s, 2H), 6.82 (s,
 1H), 3.70 (t, J = 7.2 Hz, 2H), 3.00 (t, J = 7.2 Hz,
 2H), 2.90 (s, 3H); MS (FAB) m/z 354 (MH)+; Anal.
 Calcd for C₁₈H₁₉N₅OS: C, 61.17; H, 5.42; N, 19.81.
 Found: C, 60.84; H, 5.45; N, 19.51.

15

25

30

Example 2

N'-{4-(2-Amino-4-thiazolyl)phenyl}-N-{(4-fluorophenyl)methyl}urea {1a: R^{1A}=NH₂, R^{2A}=H, A is absent, R^{3A}=H and R^{4A}=(4-fluorophenyl)methyl}

4-Fluorobenzylamine (1.80 mL, 15.8 mmol) was added (2 min) to a solution of 4-acetylphenyl isocyanate (2.50 g, 15.5 mmol) in THF (80 mL). The reaction mixture was stirred at room temperature for 2 h, then diluted with EtOAc. The resulting solution was washed serially with 1N aqueous HCl, $\rm H_2O$, saturated aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated under reduced pressure. A solution of the residue, thiourea (4.72 g, 62.0 mmol) and $\rm I_2$ (7.87 g, 31.0 mmol) in isopropanol (100 mL) was heated at reflux for 3 h. EtOAc (200 mL) was added to the cooled reaction mixture and the suspension stirred vigorously for 1 h. The suspension was

filtered, and the resulting solid was washed with EtOAc and then stirred vigorously in a mixture of 1N aqueous NaOH (-100 mL) and EtOAc (800 mL). The organic layer was washed serially with H₂O and 5 brine, then dried (MgSO₄) and concentrated under reduced pressure to give the title compound (2.23 g, 42% yield) as a white solid: M.p. 227-230°; ¹H NMR (400 MHz, DMSO-d₆) δ 8.59 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.39 (d, J= 8.4 Hz, 2H), 7.34 (dd, J = 8.6, 6.1 Hz, 2H), 7.15 (t, J = -8.6 Hz, 2H), 6.96 (s, 2H), 6.80 (s, 1H), 6.62 (t, J = 6.0 Hz, 4.28 (d, J = 6.0 Hz, 2H); MS (FAB) m/z 343 (MH)⁺; Anal. Calcd for C₁₇H₁₅N₄OSF: C, 59.64; H, 4.42; N, 16.36. Found: C, 59.67; H, 4.53; N, 16.35.

15

Example 3

 $N'-\{4-(2-Amino-4-thiazolyl)phenyl\}-N,N-dibutylurea$ (1a: $R^{1A}=NH_2$, $R^{2A}=H$, A is absent, and R^{3A} and R^{4A} each is $CH_2CH_2CH_2CH_3$)

(a) 2-Methylpropyl N-(4-Acetylphenyl) carbamate: To a 0° solution of 4'-aminoacetophenone (35 g, 259 mmol) in THF (400 mL) was added pyridine (26 mL, 324 mmol) and isobutyl chloroformate (37 mL, 285 mmol). The resulting heterogeneous mixture was stirred at 0° for 30 min and at room temperature for an additional 30 min. The reaction mixture was then diluted with EtOAc, washed serially with 10% (w/v) aqueous citric acid, 4 N aqueous HCl, H₂O, saturated aqueous NaHCO₃ and brine, then dried (MgSO₄) and concentrated under reduced pressure to yield 2-methylpropyl N-(4-acetylphenyl)carbamate (65 g, quantitative yield) as an off white solid: ¹H NMR

- 151 -

(400 MHz, CDCl₃) δ 7.95 (d, 2H, J= 8.8 Hz), 7.50 (d, 2H, J= 8.8 Hz), 6.85 (s, 1H), 3.99 (d, 2H, J= 6.7 Hz), 2.57 (s, 3H), 2.03 (m, 1H), 0.90 (d, 6H, J= 6.7 Hz); MS (FAB) m/z 236 (MH)⁺. This product was used as such in the next reaction (section (b)).

- (b) 2-Methylpropyl N-{4-(2-Amino-4-thiazolyl)-phenyl}carbamate: To a solution of the product of the preceding section (a) (19 g, 80.75 mmol) in
- isopropanol (120 mL) was added thiourea (24.6 g, 323 mmol) and iodine (20.5 g, 161.5 mmol). The resulting mixture was heated at reflux for 7 h, then diluted with EtOAc, washed serially with $\rm H_2O$ and saturated aqueous NaHCO₃. The resulting solution
- was then treated with 4N aqueous HCl and $\rm Et_2O$ and stirred vigorously. The precipitate was filtered and washed with $\rm Et_2O$. The collected solid was then treated with saturated aqueous $\rm NaHCO_3$ and extracted serially with $\rm EtOAc$ and $\rm CH_2Cl_2$. The combined
- organic extracts were washed with H₂O and brine, then dried (MgSO₄) and concentrated under reduced pressure to yield 2-methylpropyl N-{4-(2-amino-4-thiazolyl)phenyl}carbamate (12 g, 51% yield) as a pale yellow solid: ¹H NMR (400 MHz, DMSO-d₆) δ 9.63
- 25 (s, 1H), 7.70 (d, 2H, J= 8.9 Hz), 7.46 (d, 2H, J= 8.7 Hz), 6.99 (s, 2H), 6.84 (s, 1H), 3.88 (d, 2H, J= 6.9 Hz). 1.95 (m, 1H), 0.99 (d, 6H, J= 6.9 Hz); MS (FAB) m/z 292 (MH)⁺. This product was used as such in the next reaction (section (c)).

30

5

(c) The title compound: A mixture of the product of the preceding section (b) (35 g, 120.12 mmol) and dibutylamine (101 mL, 600 mmol) was heated at reflux for 4 h. The reaction mixture was then diluted with

EtOAc and washed serially with 10% (w/v) aqueous citric acid and H2O. The organic layer was diluted with aqueous HCl (4N) and Et₂O. This heterogeneous mixture was stirred and filtered. The collected solid was rinsed with Et20, treated with 10% aqueous NaOH and serially extracted with EtOAc and dichloromethane. The combined organic extracts were washed with brine, dried $(MgSO_4)$ and concentrated under reduced pressure to give 28.5 g of a light yellow solid which was purified by flash 10 chromatography (dry packed, SiO2, 1:8:8:15 mixture of MeOH, EtOAc, hexane, dichloromethane) followed by successive triturations with Et₂O until 99% purity (as determined by HPLC) was reached to yield the title compound (17.9 g, 43% yield) as an amber 15 solid: M.p. 160-162°; ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (s, 1H), 7.65 (d, 2H, J= 8.6 Hz), 7.46 (d, 2H, J=8.6 Hz), 6.96 (s, 2H), 6.81 (s, 1H), 3.27-3.31 (m, 4H), 1.47-1.50 (m, 4H), 1.26-1.33 (m, 4H), 0.90 20 (t, 6H, J=7.2 Hz); MS (FAB) m/z 347 (MH)+; Anal. Calcd for $C_{18}H_{26}N_4OS$: C, 62.40; H, 7.65; N, 16.17. Found: C, 62.26; H, 7.67; N, 16.15.

Example 4

25

 $N-\{4-(2-Amino-4-thiazolyl) phenyl\}-N',N'-dibutyl-ethanediamide (la: <math>R^{1A}=NH_2$, $R^{2A}=H$, A=C(0), and R^{3A} and R^{4A} each is $CH_2CH_2CH_3$)

To a 0° solution of exalyl chloride (479 mL, 5.49 mmol) in THF (10 mL) under nitrogen was added DIPEA (2.28 mL, 13.07 mmol) and dibutylamine (925 mL, 5.49 mmol). The resulting mixture was stirred at 0° for 5 min, whereby (dibutylamino) executyl chloride is

- 153 -

SUBSTITUTE SHEET (RULE 26)

formed, then transferred via syringe to a solution of 4-(4-aminophenyl)-2-aminothiazole (corresponding to the deprotected title compound of either Example 1 (a) or 1 (b)). The resulting mixture was stirred under nitrogen for 4 h, after which time another batch of freshly prepared (N, N-dibutylamino) oxalylchloride (prepared in the same manner and with the same amounts as above) was added to the reaction mixture. The stirring was continued for 1 h. 10 mixture was then diluted with EtOAc and extracted with 10% aqueous HCl. This aqueous extract was washed with EtOAc:Hex (1:1), then filtered. collected solid, containing the desired product as its hydrochloride salt, was treated with 2N aqueous 15 NaOH and extracted with EtOAc. This latter extract was washed with $\mathrm{H}_2\mathrm{O}$, dried (MgSO₄) and concentrated under reduced pressure to give a solid (398 mg) which was further purified by crystallization from EtOAc/MeOH to give the title compound (240 mg, 12% 20 yield) as a beige solid: M.p. 178-179°C; ¹H NMR (400 MHz, DMSO-d₆) δ 10.68 (s, 1H), 7.75 (d, 2H, J= 8.7 Hz), 7.64 (d, 2H, J= 9.0 Hz), 7.02 (s, 2H), 6.92(s, 1H), 3.33 (m, 4H), 1.50-1.60 (m, 4H), 1.33 (sixt., 4H, J= 7.5 Hz), 1.25 (sixt., 4H, J= 7.5 Hz),0.92 (t, 3H, J=7.5 Hz), 0.82 (t, 3H, J=7.5 Hz); MS 25 (FAB) m/z 375 (MH)⁺. Anal. Calcd for $C_{19}H_{26}N_4O_2S$: C, 60.94; H, 7.00; N, 14.96. Found: C, 60.82; H, 6.85; N, 14.95.

30 Example 5

In conjunction with the appropriate starting materials and intermediates, the procedures of Group 2-Examples 1 to 4 can be used to prepare other

- 154 -

compounds of Group 2-formula 1a. Examples of compounds thus prepared are listed in Tables 1 and 2 of Group 2-Example 5, together with mass spectrum data for the individual compounds and the results obtained from assays demonstrating antiherpes activity. The assays have been described hereinbefore.

- 155 -

5

		1 1	TABLE 1						
	Compound of formula		la having the structure:						T
		N - N - N - N - N - N - N - N - N - N -	A-N, RJA						
	R	=0	(P P						
M Z F K Y	wherein A is absent, R ^{4A} are designated a	(1)	R ^{2A} is H, and R ^{1A} , R ^{3A} and follows:						
No	R1A	R ³ A	R4A	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀	HSV-1 EC ₅₀	ELISA CMV EC ₅₀	PRA CMV EC ₅₀	
1	NH2	Bu	Bu	772	7	77.74	(MII)	(Mn)	
2	NH2	н	Bu	29.1	7.5	0.0	4.1	37	
			- 1		*	3.3	0.6	12	
3	NH2	н	CH ₂	340	5.2	3.6		>93*	
4	NH2	СН3	CH ₂	354	3.7	1.4	126	>144	
						_			

- 156 -

			TABLE 1					
Patro			(continued)			·		
No	R1A	R ³ A	R4A	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀	HSV-1 EC ₅₀	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
Ŋ	NH2	H	CH2	326	12	25	0.4	(MM)
9	NH2	#	CH ₂	325	6.5	3.6	2.5	55
7	NH2	Н	(4-FPh)CH ₂	343	1.9	1.3	3.2	*8
80	NH2	æ	HC CH, CH,	439	0.07	4	\ \ \ \	>103

- 157 -

	TABLE 1 (continued)	E 1 nued)					
R3A	R ⁴ A		FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀ (µM)	HSV-1 EC ₅₀ (μM)	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
Ħ	HC CH,)S	501	7.1	2.9	4.1	36
æ	H ₂ C N N		343	4.7			>48*
ж	HC CH ₃	333	E E	17	80	1.3	13
ш	СН, НС-СН, СН,	291		20	4.4	9	>32

- 158 -

			TABLE 1 (continued)					
Entry No	R1A	R3A	R4A	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀ (µM)	HSV-1 EC ₅₀ (μM)	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
13	NH2	Н	CH ₂	339	37			>4
14	Me ₃ COC(O)NH	Ме	CH ₂	454	>100	3.2	1.5	2.0
15	Me ₃ COC (0) NH	Bu	Bu	447	>100	9<	1	1.1
16	NH ₂	Н	(PhCH ₂) ₂ NCH ₂ CH ₂	458	1.6			>5*
17	NH2	н	HC≡CCH₂	273	33			>74
18	NH2	ж	N S	318				>56

- 159 -

		7	T		· · · · · · · · · · · · · · · · · · ·	\top	<u> </u>	-	1		
	PRA CMV EC ₅₀	12	7 2 7	×1×		*8^	*	* 4	185	>74.	
	ELISA CMV EC ₅₀										15.4
	HSV-1 EC ₅₀ (µM)										15.7
	HSV-1 IC ₅₀ (µM)	·	0.90	7.2		1.3	2.0	30	2.9	0.59	50
	FAB/MS (m/z) (MH) +	378	325	359/	361**	343	343	357	368	339	318
TABLE 1	R4A	CH ₂ CH ₂	PhCH ₂	(4-C1Ph)CH ₂		(3-FPh) CH ₂	(2-FPh) CH ₂	(4-FPh) CH ₂ CH ₂	(4-Me ₂ NPh)CH ₂	Ph-(S)-CHMe	
	R ³ A	н	н	Н		Н	Н	Н	Н	Н	н
	R1A	NH2	NH2	NH2		NH2	NH ₂	NH ₂	NH ₂	NH2	NH2
	Entry No	19	20	21		22	23	24	25	26	27

- 160 -

			TABLE 1 (continued)	(<i>b</i>)				
Entry No	R1A	R3A	4	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀	HSV-1 EC ₅₀	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
28	ONN				(Mrd)	(hth)	(MM)	(Mrd)
	Zunz	E	(S) - (PhCH2) CHCH2OH	369	9.9			30
29	Me3COC(0)NH	Me	CH2CH2	454				3.9
30	Me ₃ COC (O) NH	Me	Bu	405				2 2
31	Me ₃ COC(0)NH	Bt	Bu	419				2.0
32	Me ₃ COC(0)NH	носн2сн2	Bu	435				2.0
33	Me ₃ COC(0)NH	NC-CH ₂	Bu	430				2.2
34	BuNH	Bu	Bu	403				10
35	HN	Bu	Bu	424				2.2
36	HN	Bu	Bu	424				3.0
* *	Cytotoxic at this Includes isotopic		concentration of peak due to chlorine					

- 161 -

Γ	T	· · · · · · · · · · · · · · · · · · ·					
				PRA CMV EC ₅₀	(FE)	· *	12*
				ELISA CMV EC50	(mm)	2.6	10
				HSV-1 EC ₅₀	(mri)	2.9	77.0
				HSV-1 IC ₅₀	(umi)	7	1.2
				FAB/MS (m/z) (MH) +		375	443
TABLE 2	formula la having re: R ^{2A} R ^{3A} R ^{3A} R	<i>></i>	$C(0)$, R^{2A} is H, R^{1A} is and R^{4A} are designated as	R4A		Bu	CH2 Ph
	Compound of formula the structure:	RIAN	wherein A is C(0), B NH_2 , and R^{3A} and R^{4A} follows:	к3А		Bu	CH2Ph
		MZF		No		1	2

Cytotoxic at this concentration

- 162 -

070404044 1 5

Group 3: Thiazolylbenzamido Derivatives

According to another embodiment of this invention,

the present application refers to Group 3 thiazolylbenzamido derivatives having antiherpes activity.

The selective action of these compounds against
herpes viruses, combined with a wide margin of
safety, renders the compounds as desirable agents
for combating herpes infections.

The thiazolylbenzamido derivatives of the present invention can be characterized structurally by the presence of a 4-(4-thiazolyl)benzamido moiety.

- 15 Compounds possessing such a moiety have been reported previously, for example:
 - C.G. Caldwell et al., US patent 4,746,669,
 issued May 24, 1988;
- A. Bernat et al., Canadian patent application 2,046,883, published June 30, 1991;
 - A. Wissner, European patent application 458,037, published November 27, 1991;
 - D.I.C. Scopes et al., UK patent application 2
 - 276 164, published September 21, 1994;
- A. Leonardi et al., PCT patent application WO 95/04049, published February 9, 1995; and G.D. Hartman et al., PCT patent application WO 95/32710, published December 7, 1995.
- 30 The present thiazolylbenzamido derivatives can be distinguished readily from the prior art compounds in that they possess different chemical structures and biological activities.

- 163 -

SUBSTITUTE SHEET (RULE 26)

The Group 3 compounds of this application can also be represented by formula 1b:

wherein R^{1B} has the same meaning as R as defined hereinbefore and R^{2B} and R^{3B} are as defined hereinbefore.

A preferred set of Group 3 compounds of this invention is represented by Group 3-formula 1b 10 wherein R^{1B} is hydrogen, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino or (lower alkoxycarbonyl)amino; R2B is hydrogen, (1-8C)alkyl, lower alkenyl, lower alkynyl, phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl 15 monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy, lower alkyl or trifluoromethoxy; (lower cycloalkyl)-(1-3C)alkyl or (Het)-(1-3C)alkyl wherein Het is as defined hereinbefore; 2-benzimidazolylmethyl; and 20 R^{3B} is (1-8C)alkyl, phenyl-(1-3C)alkyl, phenyl-(1-3C) alkyl monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy, lower alkyl or trifluoromethoxy; 1-indanyl, 2-indanyl, (lower cycloalkyl)-(1-3C)alkyl, {1-25 hydroxy(lower cycloalkyl)}-(1-3C)alkyl or (Het)-(1-3C) alkyl wherein Het is as defined hereinbefore; or R3B is:

- 164 -

wherein R^{4B} and R^{5B} independently have the same significance as defined for R2B in the last instance and R^{6B} has the same significance as defined for R3B in the last instance; or R3B is $CH_2CH_2NR^{5B}R^{6B}$ wherein R^{5B} and R^{6B} are as defined herein; or R^{3B} is $CH(R^{7B})CH_2OH$ wherein R^{7B} has the same significance as defined for R2B in the last instance; or R^{2B} and R^{3B} together with the nitrogen 10 atom to which they are attached form a pyrrolidino, piperidino, (4-phenylmethyl)piperidinyl or (4methyl)piperizinyl; with the proviso that when R1B is (lower alkoxycarbonyl) amino then R^{2B} is hydrogen; 15 or a therapeutically acceptable acid addition salt thereof.

A more preferred set of Group 3 compounds are represented by Group 3-formula 1b wherein R1B is 20 hydrogen, amino, methylamino, dimethylamino, acetylamino or (1,1-dimethylethoxycarbonyl)amino; R^{2B} is hydrogen, methyl, ethyl, propyl, butyl, 1,1dimethylethyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-propenyl, 2-propenyl, 2-propynyl, phenylmethyl, 25 1(R)-phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, (4-chlorophenyl) methyl, (2-fluorophenyl) methyl, (3fluorophenyl)methyl, (4-fluorophenyl)methyl, (2hydroxyphenyl) methyl, (4-methoxyphenyl) methyl, (2methylphenyl) methyl, (4-methylphenyl) methyl, {(2-30 trifluoromethoxyphenyl)methyl}, (2-hydroxy-3methoxyphenyl) methyl, cyclopropylmethyl,

- 165 -

SUBSTITUTE SHEET (RULE 26)

cyclopentylmethyl, cyclohexylmethyl, 2cyclohexylethyl, (1-hydroxycyclohexyl)methyl, 2-(4morpholinyl)ethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl,2-5 furanylmethyl, 2-thienylmethyl, 3-thienylmethyl, 2thiazolylmethyl, 1-(phenylmethyl)piperidin-4-yl or 2-benzimidazolylmethyl; and R3B is methyl, ethyl, propyl, butyl, 1,1-dimethylethyl, 2-methylpropyl, 2,2-dimethylpropyl, phenylmethyl, 2-phenylethyl, (4-10 chlorophenyl)methyl, (2-fluorophenyl)methyl, (3fluorophenyl)methyl, (4-fluorophenyl)methyl, (2hydroxyphenyl) methyl, (4-methoxyphenyl) methyl, (2methylphenyl)methyl, (4-methylphenyl)methyl, {(2trifluoromethoxy)phenyl}methyl, (2-hydroxy-3-15 methoxyphenyl)methyl, 1-indanyl, 2-indanyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclohexylethyl, (1-hydroxycyclohexyl)methyl, 2-(4-morpholinyl)ethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinyl-20 methyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl, 3-thienylmethyl, 2-thiazolylmethyl, 1(R)-phenylethyl, 1(S)phenylethyl, 1(R)-cyclohexylethyl or 1(S)cyclohexylethyl;

25 or R3B is:

wherein R^{4B} is hydrogen, methyl, 1-methylethyl, phenylmethyl, cyclohexylmethyl, 3-pyridinylmethyl or (1H-imidazol-4-yl)methyl; R^{5B} has the same significance as defined for R^{2B} in the last instance

5

and R^{6B} has the same significance as defined for R^{3B} in the last instance; or R^{3B} is $CH_2CH_2NR^{5B}R^{6B}$ wherein R^{5B} and R^{6B} are defined herein; or R^{3B} is $CH(R^{7B})CH_2OH$ wherein R^{7B} has the same significance as defined for R^{4B} in the last instance; or a therapeutically acceptable acid addition salt thereof.

Another more preferred set of Group 3 compounds is 10 represented by Group 3-formula 1b wherein R1B is hydrogen, amino, methylamino, dimethylamino, acetylamino or (1,1-dimethylethoxycarbonyl)amino; R^{2B} is hydrogen, methyl, ethyl, propyl, butyl, 1,1dimethylethyl, 2-methylpropyl or 2,2-dimethylpropyl; R^{3B} is methyl, ethyl, propyl, butyl, 1,1-15 dimethylethyl, 2-methylpropyl, 2,2-dimethylpropyl, phenylmethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4fluorophenyl) methyl, (2-hydroxyphenyl) methyl, (4-20 methoxyphenyl)methyl, (2-methylphenyl)methyl, (4methylphenyl)methyl, {(2-trifluoromethoxy)phenyl)methyl, (2-hydroxy-3-methoxyphenyl)methyl, 1indanyl, 2-indanyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclohexylethyl, (1-hydroxycyclohexyl)methyl, 2-(4-morpholinyl)ethyl, 2-pyridinyl-25 methyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4pyridinyl) ethyl, 2-thienylmethyl, 3-thienylmethyl, 2-thiazolylmethyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 1(R)-cyclohexylethyl or 1(S)-cyclohexylethyl; 30 or R3B is:

- 167 -

wherein R^{4B} is hydrogen, methyl, 1-methylethyl, phenylmethyl, cyclohexylmethyl, 3-pyridinylmethyl, or (1H-imidazol-4-yl)methyl; R^{5B} is hydrogen or has the same significance as defined for R^{3B} in the last instance and R^{6B} has the same significance as defined for R^{3B} in the last instance; or R^{3B} is CH(R^{7B})CH₂OH wherein R^{7B} has the same significance as defined for R^{4B} in the last instance; or a therapeutically acceptable acid addition salt thereof.

Still another more preferred set of Group 3 15 compounds is represented by Group 3-formula 1b wherein R1B is hydrogen, amino, methylamino, dimethylamino, acetylamino or (1,1dimethylethoxycarbonyl)amino; R2B is hydrogen. methyl, ethyl, propyl, butyl, 1,1-dimethylethyl, 2-20 methylpropyl, 2,2-dimethylpropyl, phenylmethyl, 2phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4-fluorophenyl)methyl, (2-hydroxyphenyl)methyl, (4-methoxyphenyl)methyl, (2-methylphenyl)methyl, (4-methylphenyl)methyl, {(2-trifluoromethoxy)phenyl}methyl, 25 (2-hydroxy-3-methoxyphenyl)methyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclohexylethyl, (1hydroxycyclohexyl)methyl, 2-(4-morpholinyl)ethyl, 2pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinyl-30 methyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl, 3-thienylmethyl, 2-thiazolylmethyl, 1(R)-phenylethyl or 1(S)-phenylethyl; and R^{3B} is:

$$\begin{array}{ccc}
& & & \\
& & & \\
& & & \\
R^{4B} & & & R^{6B}
\end{array}$$

wherein R^{4B} is hydrogen, methyl, 1-methylethyl, phenylmethyl, cyclohexylmethyl, 3-pyridinylmethyl or (1H-imidazol-4-yl)methyl; R^{5B} has the same significance as defined for R^{2B} in the last instance and R^{6B} has the same significance as defined for R^{2B} in the last instance excluding hydrogen; or R^{3B} is Ch₂ CH₂NR^{5B}R^{6B} wherein R^{5B} and R^{6B} are as defined herein; or R^{3B} is CH(R^{7B})CH₂OH wherein R^{7B} has the same significance as defined for R^{4B} in the last instance; or a therapeutically acceptable acid addition salt thereof.

A most preferred set of Group 3 compounds is represented by Group 3-formula 1b wherein R^{1B} is amino; R^{2B} is hydrogen or phenylmethyl;

20 R^{3B} is:

wherein R^{4B} is hydrogen, R^{5B} is hydrogen or phenylmethyl and R^{6B} is phenylmethyl, 1(R)
25 phenylethyl or 1(S)-phenylethyl; or R^{3B} is CH(R^{7B})CH₂OH wherein R^{7B} is phenylmethyl and the carbon atom bearing the R^{7B} group has the (S) configuration; or a therapeutically acceptable acid addition salt thereof.

- 169 -

Still another most preferred set of Group 3 compounds is represented by Group 3-formula 1b wherein \mathbb{R}^{1B} is amino or (1,1-

- dimethylethoxycarbonyl)amino; R^{2B} is hydrogen, 2-propynyl, phenylmethyl, 2-phenylethyl, cyclopropylmethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-furanylmethyl, 1-
- 10 (phenylmethyl)piperidin-4-yl or 2benzimidazolylmethyl; and R^{3B} is phenylmethyl or (3fluorophenyl)methyl;
 and R^{3B} is:

$$\begin{array}{ccc} & & & \\ & & &$$

15

wherein R^{4B} is hydrogen, R^{5B} is hydrogen, methyl, phenylmethyl, (2-hydroxyphenyl)methyl, (2-methylphenyl)methyl, ((2-trifluoromethoxy)phenyl)-methyl, (2-hydroxy-3-methoxyphenyl)methyl, (1-hydroxycyclohexyl)methyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl or 2-thiazolylmethyl; and R^{6B} is phenylmethyl or 1(S or R)-phenylethyl; or R^{3B} is CH₂CH₂NR^{5B}R^{6B} wherein R^{5B} is phenylmethyl and R^{6B} is phenylmethyl or 1(S or R)-phenylethyl; or R^{3B} is CH(R^{7B})CH₂OH wherein R^{7B} is phenylmethyl and the carbon atom bearing the R^{7B} group has the (S) configuration; or a therapeutical-

30 Included within the scope of this invention is a pharmaceutical composition comprising an antiherpes

ly acceptable acid addition salt thereof.

virally effective amount of a compound of Group 3 as defined herein, or a therapeutically acceptable acid addition salt thereof, and a pharmaceutically or veterinarily acceptable carrier.

5

10

Still another aspect of this invention involves a method for treating acyclovir-resistant herpes infections in a mammal which comprises administering to the mammal an anti-acyclovir-resistant herpes effective amount of a compound of Group 3 as defined herein, or a therapeutically acceptable acid addition salt thereof.

Process for Preparing the Compounds of Group 3

15

The compounds of Group 3 can be prepared by a variety of processes. Descriptions of some of these methods are found in standard textbooks such as "Annual Reports In Organic Synthesis-1994", P.M.

- Weintraub et al., Eds., Academic Press, Inc., San Diego, CA, USA, 1994 (and the preceding annual reports), "Vogel's Textbook of Practical Organic Chemistry", B.S. Furniss et al., Eds., Longman Group Limited, Essex, UK, 1986, and "Comprehensive Organic
- 25 Synthesis", B.M. Trost and I. Fleming, Eds., Pergamon Press, Oxford, UK, 1991, Volumes 1 to 8.

Generally speaking, the compounds of Group 3-formula 1b can be prepared by a process selected from the following processes (a) or (b):

(a) coupling a compound of the formula

- 171 -

wherein R^{1B} is as defined herein, with an amine of the formula:

$$R^{2B}_{N} R^{3B}$$

5

wherein R^{2B} and R^{3B} are as defined herein, to obtain the corresponding compound of formula 1b; or

(b) coupling 4-acetylbenzoic acid with an amine of the formula:

wherein R^{2B} and R^{3B} are as defined herein, to obtain the corresponding benzamide derivative of the formula:

and either (i) reacting the latter benzamide 20 derivative with Br_2 , Cl_2 or I_2 whereby the methyl ketone moiety of the benzamide derivative is converted to the corresponding α -haloketone and reacting the resulting α -haloketone with a

thioamide or thiourea of the formula $H_2N-C(S)-R^{1AAA}$ wherein R^{1AAA} is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino to obtain the corresponding compound of Group 3-formula 1b wherein R^{1B} is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino, and R^{2B} and R^{3B} are as defined herein; or (ii) reacting the latter benzamide derivative with a thiourea derivative of

lower alkylamino or di(lower alkyl)amino, in the presence of Br₂, Cl₂ or I₂ to obtain the corresponding compound of Group 3-formula 1b wherein R^{1B} is amino, lower alkylamino or di(lower alkyl)amino and R^{2B} and R^{3B} are as defined herein;

the formula $H_2N-C(S)-R^{1AAA}$, wherein R^{1AAA} is amino,

and if desired, effecting standard transformations to the products of processes (a) and (b) to obtain other compounds of Group 3-formula 1b; and further, if desired, converting the compound of Group 3-formula 1b into a therapeutically acceptable acid addition salt.

More explicitly, a practical and convenient procedure to prepare compounds of Group 3-formula 1b is illustrated by Group 3-scheme 1:

25

30

- 173 -

According to Group 3-scheme 1, 4-acetylbenzoic acid (2) is coupled with an amine derivative of formula 3, wherein R^{2B} and R^{3B} are as defined herein, to give a corresponding benzamide derivative of formula 4.

The coupling of 4-acetylbenzoic acid (2) and the amine derivative of formula 3 is effected by the classical dehydrative coupling of a free carboxyl of one reactant with the free amino group of the other reactant in the presence of a coupling agent to form a linking amide bond, as described hereinbefore.

15

20

10

The benzamide derivative of formula 4 is converted to the thiazolyl derivative of formula 5 wherein Rlaaa hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino by reacting the compound of formula 4 with Br₂, Cl₂ or I₂ whereby the methyl ketone moiety of the compound of formula 4 is converted to the corresponding α -haloketone. This

 α -haloketone derivative is then reacted with a thioamide or thiourea of the formula $H_2N-C(S)-R^{1AAA}$ wherein R^{1AAA} is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino according to the classical reaction described by R.H. Wiley et al, Organic Reactions 1951, 6, 367-374 for preparing thiazole compounds from thioamides or thioureas and α -halocarbonyl compounds, to obtain the corresponding thiazolyl derivative of formula 5.

- Alternatively, the benzamide derivative of formula 4 can be directly converted to the thiazolyl derivative of formula 5 wherein RlAAA is amino, lower alkylamino or di(lower alkyl)amino by heating the benzamide derivative of formula 4 with an
- appropriate thiourea derivative of the formula $H_2N-C(S)-R^{1AAA}$, wherein R^{1AAA} is amino, lower alkylamino or di(lower alkyl)amino, in the presence of Br_2 , Cl_2 or I_2 according to the classical methods of R.M. Dodson and L.C. King, J. Amer. Chem Soc. 1945, 67,
- 20 2242. The thiazolylbenzamide derivative of formula 5, albeit a compound of Group 3-formula 1b, can also serve as an intermediate for further elaboration by standard methods to yield other compounds of Group 3-formula 1b (for example, the compound of formula 5
- wherein Rlama is amino can serve as an intermediate for transformation by standard methods to compounds of Group 3-formula 1b wherein RlB is lower alkanoylamino or lower alkoxycarbonyl).
- 30 Another general procedure for preparing compounds of Group 3-formula 1b can be represented by Group 3-scheme 2:

- 175 -

Group 3 - Scheme 2

PG
$$R^{4B}$$
 OH R^{5B} R^{5B} R^{6B} R^{5B} R^{6B} R^{4B} R^{5B} R^{6B} R^{4B} R^{5B} R^{6B} R^{4B} R^{5B} R^{6B} R^{6B}

According to Group 3-scheme 2, an N-protected amino acid of formula 6, wherein PG is an amino protecting group and R^{2B} and R^{4B} are as defined herein, is reacted with an amine derivative of formula 7 wherein R^{5B} and R^{6B} are as defined herein, to give the amide derivative of formula 8. The amino protecting group PG of the amide of formula 8 is then removed to give the compound of formula 9.

The compound of formula 9 can then be used to

15 prepare compounds of Group 3-formula 1b by simply repeating the process outlined in Group 3-scheme 1 and replacing the amine of formula 3 in Group 3-scheme 1 with the amine of formula 9 from Group 3-scheme 2.

20

Examples of amino protective groups suitable for use in the above schemes include benzyloxycarbonyl,

tert-butoxycarbonyl, 4-methoxybenzyloxycarbonyl or 2,2,2-trichloroethoxycarbonyl.

- Other starting materials for the preceding processes are known or can be readily prepared from known starting materials. 4-Acetylbenzoic acid (2) of Group 3-scheme 1 is available from the Aldrich Chemical Co., Milwaukee, WI, USA.
- The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the
- disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, the reaction can be successfully performed by conventional modification known to those skilled in the art, e.g. by
- appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, or by modification illustrated in the examples herein.
- Furthermore, if desired, the compound of Group 3formula 1b can be obtained in the form of a
 therapeutically acceptable acid addition salt. Such
 salts can be considered as biological equivalents of
 the compounds of Group 3-formula 1b. Examples of
 such salts are those formed with budgeshlopin and
- 30 such salts are those formed with hydrochloric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid or citric acid.

- 177 -

Antiherpes Activity

The antiviral activity of the compounds of Group 3formula 1b, or their corresponding therapeutically

5 acceptable acid addition salts, can be demonstrated
in the same manner as described herein for the
compounds of Group 1-formula 1. Likewise, the
compounds of Group 3-formula 1b, or their
corresponding therapeutically acceptable acid

10 addition salts, can be formulated and employed as
antiviral agents in the same manner as described
herein for the compounds of Group 1-formula 1.

The following examples further illustrate this
invention. Temperatures are given in degrees
Celsius. Solution percentages or ratios express a
volume to volume relationship, unless stated
otherwise. Nuclear magnetic resonance spectra were
recorded on a Bruker 400 MHz spectrometer; the
chemical shifts (δ) are reported in parts per
million. The concentrations for the optical
rotations are expressed in grams of the compound per
100 mL of solution. Abbreviations or symbols used
in the examples are as defined hereinbefore.

25

GROUP 3 EXAMPLES

Example 1

30 4-(2-Amino-4-thiazolyl)-N-{2-oxo-2-{di(phenyl-methyl)amino}ethyl}benzamide (1b: R^{1B}=NH₂, R^{2B}=H, R^{3B}=

 $R^{4B}=H$, $R^{5B}=$ phenylmethyl and $R^{6B}=$ phenylmethyl)

- 5 (a) tert-Butyl N-{2-0xo-2-{di(phenylmethyl)amino}-ethyl}carbamate: To a solution of Boc-glycine (6.0 g, 34.2 mmol) (Aldrich Chemical Co., Milwaukee, WI, USA) in DMF (100 mL) was added successively DIPEA (17.9 mL, 103 mmol), dibenzylamine (6.25 mL, 32.5
- mmol) (Aldrich Chemical Co., Milwaukee, WI, USA) and BOP.PF₆ (15.14 g, 34.2 mmol). The resulting solution was stirred at room temperature for 2 h, then diluted with EtOAc, washed serially with H₂O, 4N aqueous HCl, saturated aqueous NaHCO₃, and brine,
- dried (MgSO₄) and concentrated under reduced
 pressure to give tert-butyl N-{2-oxo-2 {di(phenylmethyl)amino}ethyl}carbamate (11.39 g, 99%
 yield) as an off white solid: ¹H NMR (400 MHz, DMSO-d₆) δ 7.21-7.39 (m, 10H), 6.86 (t, 1H, J= 5.7 Hz),
- 20 4.50 (s, 2H), 4.48 (s, 2H), 3.87 (d, 2H, J= 5.7 Hz), 1.37 (s, 9H); MS (FAB) m/z 355 (MH)+.
- (b) N,N-Di (phenylmethyl) -2-aminoacetamide Hydrochloride: To a solution of the product of the
 25 preceding section (a) (2.5 g, 7.03 mmol) in 1,4-
- dioxane (10 mL) was added 4N HCl in 1,4-dioxane (8.8 mL, 35.2 mmol). The resulting solution was stirred at room temperature for 5 h, then concentrated under reduced pressure (coevaporation with 1:1
- 30 Et₂O/benzene) to give N, N-di(phenylmethyl)-2aminoacetamide hydrochloride (2.05 g, 99% yield) as

- 179 -

a light yellow foam: $^1{\rm H}$ NMR (400 MHz, DMSO-d₆) δ 8.24 (s, 2H), 7.22-7.41 (m, 10H), 4.54 (s, 4H), 3.90 (s, 2H); MS (FAB) m/z 255 (MH)+. This product was used as such in the next reaction (section (c)).

5

10

- (c) N-{2-Oxo-2-{di(phenylmethyl)amino}ethyl}-4-acetylbenzamide: To a solution of 4-acetylbenzoic acid (1.21 g, 7.37 mmol) in DMF (35 mL) was added successively the product of the preceding section (b) (2.03 g, 7.0 mmol), DIPEA (4.3 mL, 24.5 mmol) and BOP.PF₆ (3.25 g, 7.37 mmol). The resulting solution was stirred at room temperature for 2 h, then diluted with EtOAc, washed serially with H_2O , 4N aqueous HCl, saturated NaHCO₃, and brine, dried (MgSO₄) and concentrated under reduced pressure to
- (MgSO₄) and concentrated under reduced pressure to give N-{2-oxo-2-{di(phenylmethyl)amino}ethyl}-4-acetylbenzamide (2.70 g, 99% yield) as a light yellow foam: ¹H NMR (400 MHz, DMSO-d₆) δ 8.89 (t, 1H, J= 5.7 Hz), 8.05 (d, 2H, J= 8.4 Hz), 8.00 (d,
- 20 2H, J= 8.4 Hz), 7.24-7.44 (m, 10 H), 4.61 (s, 2H),
 4.51 (s, 2H), 4.25 (d, 2H, J= 5.7 Hz), 2.52 (s, 3H);
 MS (FAB) m/z 401 (MH)+. This product was used as
 such in the next reaction (section (d)).
- 25 (d) The title compound: To a solution of the product of the preceding section (c) (2.7 g, 6.74 mmol) in isopropanol (14 mL) was added iodine (3.55 g, 14.0 mmol) and thiourea (2.13 g, 28.0 mmol). The resulting mixture was heated at reflux for 18 h,
- then diluted with EtOAc/Et₂O and filtered. The collected solid was then treated with 1N aqueous NaOH and extracted with EtOAc. The EtOAc extract was washed with brine, and dried (MgSO₄). Concentrated under reduced pressure, followed by

trituration with EtOAc, gave the title compound (1.58 g, 50% yield) as a white solid: ^1H NMR (400 MHz, DMSO-d₆) δ 8.66 (t, 1H, J= 5.7 Hz), 7.88 (s, 4H), 7.22-7.42 (m, 10H), 7.18 (s, 1H), 7.09 (s, 2H), 4.60 (s, 2H), 4.51 (s, 2H), 4.23 (d, 2H, J= 5.7 Hz); MS (FAB) m/z 457 (MH)⁺.

Example 2

4-(2-Amino-4-thiazolyl)-N-{2-0xo-2-{(phenylmethyl)-{1(S)-phenylethyl}amino}ethyl}-N-(phenylmethyl)-benzamide (lb: R^{1B}=NH₂, R^{2B}=phenylmethyl, R^{3B} = 0 p^{5B}

- 15 $R^{4B}=H$, $R^{5B}=$ phenylmethyl and $R^{6B}=1$ (S)-phenylethyl)
 - (a) 2-(phenylmethyl)amino-N-phenylmethyl-N-{1(S)-phenylethyl}acetamide hydrochloride: By following the procedure of Example 1(a) but replacing
- 25 The Boc group was removed following the procedure of Example 1(b) to give N-{2-oxo-2-{(phenylmethyl){1(S)-phenylethyl}amino}ethyl)carbamate hydrochloride, which was subjected to reductive amination with benzaldehyde according the procedure
- 30 of R.F. Borch, Org. Synth., 1972, 52, 124, to give

- 181 -

2-(phenylmethyl)amino-N-phenylmethyl-N-{1(S)-phenyl-ethyl)acetamide hydrochloride.

- (b) The title compound: To a solution of 4-3 acetylbenzoic acid (450 mg, 2.74 mmol) in DMF (15 mL) was added successively 2-(phenylmethyl)amino-N-phenylmethyl-N-{(1(S)-phenylethyl)acetamide hydro-chloride (1.02 g, 2.60 mmol), DIPEA (1.43 mL, 8.22 mmol) and BOP.PF₆ (1.21 g, 2.74 mmol). The
- resulting solution was stirred at room temperature for 4 h, then diluted with EtOAc, washed serially with H₂O, 4N aqueous HCl, saturated aqueous NaHCO₃, and brine, dried (MgSO₄) and concentrated under reduced pressure to give 4-acetyl-N-(phenylmethyl)-
- N-{2-0xo-2-{(phenylmethyl)}{1(S)-phenylethyl}amino}-ethyl}benzamide as a light yellow foam. To a solution of this foam in isopropanol (30 mL) was added I₂ (1.31 g, 5.2 mmol) and thiourea (792 mg, 10.4 mmol). The resulting mixture was heated at
- reflux for 18 h, then diluted with EtOAc, washed serially with saturated aqueous NaHCO3, H2O and brine, dried (MgSO4) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO2, EtOH:CHCl3:EtOAc:hexane,
- 25 1:2:2:10) to give the title compound (648 mg, 45% yield) as an off-white solid: ¹H NMR (400 MHz, DMSO-d₆) (mixture of 4 rotamers) δ, 7.85-7.82 (m, 2H), 7.42-6.91 (m, 20H), 5.89-5.87, 5.86-5.79, 5.34-5.30, 5.02-4.96 (4 m, 1H), 4.80-4.68, 4.61-4.47, 4.41-
- 30 4.34, 4.27-4.19, 4.10-3.96, 3.80-3.76 (6 m, 6H), 1.39-1.33, 1.17 (2 m, 3H); MS (FAB) m/z 561 (mH)+; Anal. Calcd for C₃₄H₃₂N₄O₂S: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.20; H, 5.69; N, 9.86.

Example 3

In conjunction with the appropriate starting materials and intermediates, the procedures of Group 3-Examples 1 and 2 can be used to prepare other compounds of Group 3-formula 1b. Examples of compounds thus prepared are listed in Table 1 and 2 of Group 3-Example 3, together with mass spectrum data for the individual compounds and the results obtained from assays demonstrating antiherpes activity. The assays have been described hereinbefore.

- 183 -

R3B (m/z) (mH) ⁺ (μM) (μM) PhCH ₂ 3-FPh)CH ₂ 328 490 >30 Bu 332 >100 338 (13) (13) (13) (13) (14) (14) (14) (14) (14) (14) (14) (14	Compound of fastructure:	formula 1b having the R S IS NH2 and R ^{2B} and R ^{3B} are					
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	<u> </u>	follows:	FAB/MS	HSV-1	HSV-1	ELISA CMV	PRA
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$			(MH) +	(Mt)	(μη)	(µM)	EC50
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		PhCH ₂	310	158	>30	5.5	09
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		(3-FPh)CH ₂	328	490	>30	2.5	38
378 13 13 13 CH ₂ C(0)NHCH ₂ Ph 367 20 5.0			332	>100		40	·
367 20 5.0	н	$\bigcup_{c} \bigcup_{Z_{i}}$	378	13	13	21	·
		CH ₂ C (O) NHCH ₂ Ph	367	20	5.0	46	>2.5**
$CH_2C(0)N(CH_2Ph)_2$ 457 2.1 0.35 0.4		$CH_2C(0)N(CH_2Ph)_2$	457	2.1	0.35	0.4	12

- 184 -

		T	
	PRA CMV EC50	8.7	. 4
	ELISA CMV EC ₅₀	3.9	0.5
	HSV-1 EC ₅₀	1.0	12.6
	HSV-1 IC ₅₀	1.9	>50
	FAB/MS (m/z) (MH) +	471	561
TABLE 1 (continued)	Ŗ ^{3В} .	$CH_2C(0)N \longrightarrow CH_3$	CH ₂ C (O) N CH ₃
	R2B	x .	PhCH ₂
Roters	No	7	ω

- 185 -

TABLE 1 (continued)	R3B (m/z) HSV-1 HSV-1 CMV CM	25 >109	HC >50 1.0 >48	HC >50
TABLE (continue		\ /		1 \ /
	R2B	æ	Z.	Ħ
	No	0	10	11

- 186 -

- 187 -

	TABLE 1
	Sontinued) FAB/MS HSV-1 HSV-1 CMV (m/z) EC50 EC50 (MH) + (μM) (μM) (μM) (μM) Some 593 FAB/MS HSV-1 CMV CMV CMV (MH) (μM) (μM) (μM) Some 593 FAB/MS HSV-1 HSV-1 CMV CMV CMV CMV (MH) (μM) (μM) FAB/MS FAB (MH) + (μM) (μM) (μM) (μM) Some 593 FAB/MS HSV-1 HSV-1 CMV
PhCH ₂ PhCH ₂ CH ₂ C (O) N (CH ₂ Ph) CH ₂ PhCH ₂ CH ₂ C (O) N (CH ₂ Ph) CH ₂ PhCH ₂ CH ₂ C (O) N (CH ₂ Ph) CH ₂	Some 593 OME 593 September FAB/MS HSV-1 HSV-1 CMV CMV (MM) (µM) (µM)
R2B R3B FAB/MS (m/z) (mH) + (mM) HSV-1 (LM) ELISA (LM) PhCH2 CH2C(0)N(CH2Ph)CH2 S S S S S S S S S S S S S S S S S S S	Sontinued) FAB/MS HSV-1 HSV-1 CMV (m/z) IC ₅₀ EC ₅₀ EC ₅₀ (MH) ⁺ (µM) (µM) (µM) S OME 593 H 569 548
R2B $\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Sontinued) FAB/MS HSV-1 HSV-1 CMV (m/z) IC ₅₀ EC ₅₀ EC ₅₀ (MH) + (µM) (µM) (µM) S
R2B PhCH ₂ $CH_{2}C(O) N (CH_{2}Ph) CH_{2} \longrightarrow S_{2}$ $CH_{2}C(O) N (CH_{2}Ph) CH_{2} \longrightarrow S_{3}$ $CH_{2}C(O) N (CH_{2}Ph) CH_{2} \longrightarrow S_{4}$	Sontinued) FAB/MS HSV-1 HSV-1 CMV (m/z) (MH) + (μM) (μM) (μM) S OMe 593
R2B R3B FAB/MS HSV-1 HSV-1 CMV CMT CMJ Ph.) CH ₂ CH ₂ C(O) N (CH ₂ Ph.) CH ₂ S	Continued FAB/MS HSV-1 HSV-1 CMV CMV (M/Z) IC50 EC50
R2B R3B (m/z) $(m/z$	Sontinued) FAB/MS HSV-1 HSV-1 CMV (m/z) IC ₅₀ EC ₅₀ EC ₅₀ (MH) ⁺ (μM) (μM) (μM) S OMe 593
R2B R3B RMS HSV-1 HSV-1 CMV (MH) $\frac{(Continued)}{(MH)^{+}}$ ($\frac{(m/z)}{(MH)^{+}}$ ($\frac{(m/z)}{(MH)^{+}}$ ($\frac{(m)}{(MM)}$ ($($	Sontinued) FAB/MS HSV-1 HSV-1 CMV (m/z) IC50 EC50 EC50 (MH) + (μM) (μM) (μM) S
R2B R3B FAB/MS HSV-1 HSV-1 CMV (m/z) IC50 EC50 (MH) (µM) (µM) (µM) (µM)	FAB/MS HSV-1 HSV-1 CMV CMV (MH) + (μM)
R2B R3B FAB/MS HSV-1 HSV-1 CMV (MH) + (μM) (μM) (μM) (μM) (μM)	(continued) FAB/MS HSV-1 HSV-1 CMV (m/z) IC50 EC50 EC50 (MH) + (µM) (µM) (µM)
(continued) R2B R3B R3B R3B R3B R3B R3B R3B R5D R5D EC50	(continued) FAB/MS HSV-1 HSV-1 CMV (m/z) IC50 EC50 EC50
	(continued)

- 188 -

FAB/MS HSV-1 HSV-1 (m/z) IC ₅₀ EC ₅₀ (MH) + (μM) (μM) (μM) (μM) 563			TABLE 1					
R2B R3B R3B FAB/MS HSV-1 (MH) + (μ M) HSV-1 (μ M) HSV-1 (μ M) HSV-1 (μ M) HSV-1 (μ M) PhCH2 CH2C(0)N(CH2Ph)CH2 563 631 μ M) PhCH2 CH2C(0)N(CH2Ph)CH2 631 μ M) PhCH2 CH2C(0)N(CH2Ph)CH2 561 μ M)	1 2 2		(continued)					
PhCH ₂ $CH_{2}C(0)N(CH_{2}Ph)CH_{2}$ $CH_{2}C(0)N(CH_{2}Ph)CH_{2}$ $CH_{2}C(0)N(CH_{2}Ph)CH_{2}$ $CH_{2}C(0)N(CH_{2}Ph)CH_{2}$ $CH_{2}C(0)N(CH_{2}Ph)CH_{2}$ $CH_{2}C(0)N(CH_{2}Ph)CH_{2}$ $CH_{2}C(0)N(CH_{2}Ph)CH_{2}$	Ellery			FAB/MS	HSV-1	HSV-1	ELISA	PRA
PhCH ₂ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow 631$ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow 631$ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow CH_3$	Q Z	R ^{2B}	R ^{3B}	(m/z)	IC ₅₀	EC ₅₀	EC ₅₀	EC ₅₀
PhCH ₂ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow F_3CO$ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow CH_3$ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow CH_3$ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow CH_3$ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow CH_3$				(MH)	(MH)	(MII)	(MI)	(MI)
PhCH ₂ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow F_3CO$ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow CH_3$ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow CH_3$	24	PhCH ₂	OH	563				6.1
PhCH ₂ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow CH_3$ $CH_2C(0)N(CH_2Ph)CH_2 \longrightarrow CH_3$			$CH_2C(0)N(CH_2Ph)CH_2$					
$CH_{2}C(0)N(CH_{2}Ph)CH_{2}$ $PhCH_{2}$ $CH_{2}C(0)N(CH_{2}Ph)CH_{2}$	25	PhCH ₂	F3CO	631				3.8
PhCH ₂ CH ₂ C(0)N(CH ₂ Ph)CH ₂			$CH_2C(0)N(CH_2Ph)CH_2$					
$CH_2C(0)N(CH_2Ph)CH_2$	26	PhCH ₂	ĥЭ	561				5
			$CH_2C(0)N(CH_2Ph)CH_2$					

- 189 -

TABLE 1 (continued)	FAB/MS HSV-1 HSV-1 (m/z) IC50 EC50	$CH_2C(O)N$, Me $S61$ (μM) (μM) (μM)	CH ₂ C(O)N\Me 485
Rnfrv	R2B	PhcH ₂ CH ₂ C(0)N	PhCH ₂
Ē	No	27	28

- 190 -

	T		
	PRA CMV EC ₅₀	(IIM)	21
·	ELISA CMV EC ₅₀	(EH)	
	HSV-1 EC50		
	HSV-1 IC ₅₀		
	FAB/MS (m/z) (MH) +	562	562
TABLE 1 (continued)	R3B	CH ₂ C(0)N Me	CH ₂ C (0) N Me
	R2B	PhCH ₂	PhCH ₂
Part T	NO	29	30

- 191 -

SUBSTITUTE SHEET (RULE 26)

		- STORE					
Entry	,	(continued)					
No	R ² B	R3B	FAB/MS (m/z) (MH) +	HSV-1 IC ₅₀	HSV-1 EC ₅₀	ELISA CMV EC ₅₀	PRA CMV EC ₅₀
31	CH2CH2	CH ₂ C(0)N(CH ₂ Ph) ₂	562	(wm)	(Mrl)	(мп)	(µм) 16
32	Ph-(S)-CHMe	CH ₂ C(0)N(CH ₂ Ph) ₂	561				
33	Ph-(R)-CHMe	$CH_2C(0)N(CH_2Ph)_2$	561				4.5 0.4
34	I N CH		587				7.0
35	0 OH2	CH ₂ C(O)N(CH ₂ Ph) ₂	537				7.7

- 192 -

TABLE 1 (continued)	1 HSV-1 EC50	(MII) (MII) (MII)	CH ₂ CH ₂ C(0)N Me
	R2B	N N	OH OH
Entry	No	36	37

- 193 -

	PRA CMV EC ₅₀		14
	ELISA CMV EC50	(End)	
	HSV-1 EC ₅₀		
	HSV-1 IC50		
	FAB/MS (m/z) (MH) +	562	576
TABLE 1 (continued)	R3B	CH ₂ C (0) N Me	CH ₂ C (0) N Me
	R2B	QH CH	N CH2CH2
	No	œ r	3.9

- 194 -

	PRA CMV EC ₅₀	3.0	5.3
	ELISA CMV EC ₅₀		
	HSV-1 EC ₅₀		
	HSV-1 IC ₅₀		
	FAB/MS (m/2) (MH) ⁺	575	601
TABLE 1 (continued)	R ³ B	CH ₂ C (0) N Me	CH ₂ C (0) N Me
	R2B .	Ph- (R) -СНМе	T CH ₂
	No	40	41

- 195 -

Γ			
	PRA CMV EC ₅₀	(µm)	12
	ELISA CMV EC ₅₀	(End)	
	HSV-1 EC ₅₀		
	HSV-1 IC50		
	FAB/MS (m/z) (MH) +	509	525
TABLE 1	R ^{3B}	CH ₂ C (0) N Me	CH ₂ C (O) N Me
	R ^{2B}	HC≡C-CH2	
	Entry No	42	43

- 196 -

	PRA CMV EC ₅₀	(µм)	5.5
	ELISA CMV EC ₅₀	(Ми)	
	HSV-1 EC50	(мт)	
	HSV-1 IC ₅₀	(MII)	
	FAB/MS (m/z)	575	644
TABLE 1	R3B	CH ₂ C (0) N Me	CH ₂ C(0)N Me
	R2B	PhCH2CH2	1-(phenyl- methyl)- piperidin-4- yl
	Entry No	44	45

- 197 -

SUBSTITUTE SHEET (RULE 26)

- 198 -

- 199 -

,		HSV-1 CMV CMV EC50 EC50 EC50		
		HSV-1 IC ₅₀	(MH)	
		FAB/MS (m/z) (MH) +		547
TABLE 1	(pantitorino)	R ^{3B}		CH ₂ CH ₂ N Me
		R2B		РһСН2
	Entry	No	5.1	

 $m R^{2B}$ and $m R^{3B}$ together with the N atom to which they are attached form a

Cytotoxic at this concentration

			TABLE 2					
	Compound of	formula	1b having the structure:					
		R 18 N	N.R ^{2B}					
E Z		S						
E K Y	wherein R ^{lB} , follows:	R ^{2B} and	R ^{3B} are designated as		·			
NO	R1B	R ^{2B}	R3B	FAB/MS (m/z)	HSV-1 IC ₅₀	HSV-1 EC50	ELISA CMV EC50	PRA CMV EC ₅₀
-				(HM)	(Мп)	(ши)	(ми)	(Mid)
7	Me3COC(O)NH	H	$CH_2C(0)N(CH_2Ph)_2$	557				<1.2
7	Me ₃ COC (O) NH	×	CH ₂ C(0)N CH ₃	571				<1.2
			>				-	

- 201 -

Group 4: Thiazolylphenoxyacetamide Derivatives

According to another embodiment of this invention, the present application refers to Group 4 thiazolyl-phenoxyacetamide derivatives having antiherpes activity. The selective action of these compounds against herpes viruses, combined with a wide margin of safety, renders the compounds desirable agents for combating herpes infections.

10

5

The thiazolylphenoxyacetamide derivatives of the present invention can be characterized structurally by the presence of a (4-thiazolylphenoxy)acetamide moiety. Compounds possessing such a moiety have been reported previously, for example:

A. Wissner, European patent application 458,037, published November 27, 1991; and A. Wissner, US patent 5,077,409, issued December 31, 1991

20

15

The present thiazolylphenoxyacetamide derivatives can be distinguished readily from the prior art compounds in that they possess different chemical structures and biological activities.

25

The Group 4 thiazolylphenoxyacetamide derivatives of this invention can also be represented by formula 1c:

$$R^{\frac{1C}{S}} \stackrel{\text{OCH}_2C (O) NR^{2C}R^{3C}}{}$$
(1c)

wherein R^{1C} has the same meaning as R as defined hereinbefore and R^{2C} and R^{3C} are as defined hereinbefore.

5 A preferred set of Group 4 compounds of this invention are represented by Group 4-formula 1c wherein R1C is hydrogen, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino or (lower alkoxycarbonyl)amino; R2C and R3C each independently is hydrogen, lower alkyl, phenyl, 10 phenyl-(1-3C)alkyl or phenyl-(1-3C)alkyl monosubstituted or disubstituted on the aromatic portion thereof with a substituent selected independently from the group consisting of halo, hydroxy, lower 15 alkoxy and lower alkyl; 1-indanyl, diphenylmethyl, lower cycloalkyl, (lower cycloalkyl)-(1-3C)alkyl or (Het)-(1-3C)alkyl wherein Het is as defined hereinbefore; or a therapeutically acceptable acid addition salt thereof.

20

A more preferred set of Group 4 compounds is compounds of Group 4-formula 1c wherein R1C is amino, methylamino, acetylamino or (1,1-dimethylethoxycarbonyl)amino; R^{2C} and R^{3C} are independently hydrogen, methyl, ethyl, propyl, butyl, 1,1-di-25 methylethyl, 2,2-dimethylpropyl, phenyl, phenylmethyl, 1(R) - or 1(S) -phenylethyl, 2-phenylethyl, {4-(1,1-dimethylethyl)phenyl}methyl, (4-chlorophenyl)methyl, (3-fluorophenyl)methyl, (4-fluoro-30 phenyl)methyl, (4-methoxyphenyl)methyl, 1-indanyl, diphenylmethyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, 2-cyclohexylethyl, 2-(4-morpholinyl)ethyl, 2-pyridinylmethyl, 3pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)-

- 203 -

WO 97/24343 PCT/US96/1913: -

ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl or 3-thienylmethyl; or a therapeutically acceptable acid addition salt thereof.

- A most preferred set of Group 4 compounds is represented by Group 4-formula 1c wherein R^{1C} is amino, R^{2C} is hydrogen or phenylmethyl, and R^{3C} is phenyl, phenylmethyl, 2-phenylethyl, {4-(1,1-dimethylethyl)phenyl}methyl, (3-fluorophenyl)methyl, 1-indanyl, cycloberyl cycloberyl
- 1-indanyl, cyclohexyl, cyclohexylmethyl, 2pyridinylmethyl, 3-pyridinylmethyl or 4pyridinylmethyl; or a therapeutically acceptable
 acid addition salt thereof.
- Another most preferred set of Group 4 compounds is represented by Group 4-formula 1c wherein R^{1C} is amino, methylamino or acetylamino, R^{2C} is hydrogen or phenylmethyl, and R^{3C} is phenyl, phenylmethyl, cyclohexyl or cyclohexylmethyl; or a therapeutically acceptable acid addition salt thereof.
- Included within the scope of this invention is a pharmaceutical composition comprising an antiherpes virally effective amount of a compound of Group 4-formula 1c, or a therapeutically acceptable acid addition salt thereof, and a pharmaceutically or veterinarily acceptable carrier.
- Still another aspect of this invention involves a
 method for treating acyclovir-resistant herpes
 infections in a mammal which comprises administering
 to the mammal an anti-acyclovir-resistant herpes
 effective amount of a compound of Group 4-formula 1c

as defined herein, or a therapeutically acceptable acid addition salt thereof.

Process for preparing the Compounds of Group 4

5

10

15

20

30

The compounds of Group 4 can be prepared by a variety of processes involving known methods. Description of the methods are found in standard textbooks such as "Annual Reports In Organic Synthesis - 1994", P.M. Weintraub et al., Eds., Academic Press, Inc., San Diego, CA, USA, 1994 (and the preceding annual reports), "Vogel's Textbook of Practical Organic Chemistry", B.S. Furniss et al., Eds., Longman Group Limited, Essex, UK, 1986, and "Comprehensive Organic Synthesis", B.M. Trost and I. Fleming, Eds., Pergamon Press, Oxford, UK, 1991, Volumes 1 to 8.

A general process can be represented by Group 4-scheme 1:

Group 4 - Scheme 1

wherein R^{1C} , R^{2C} and R^{3C} are as defined herein.

According to scheme 1, the thiazolylphenoxyacetic acid of formula 2 is coupled with a primary or secondary amine of formula 3 to give the corresponding compound of Group 4-formula 1c. This

- 205 -

SUBSTITUTE SHEET (RULE 26)

coupling is effected by the classical dehydrative coupling of a free carboxyl of one reactant with the free amino group of the other reactant in the presence of coupling agent to form a linking amide bond, as described hereinbefore.

In turn, the thiazolylphenoxyacetic acid of formula 2 wherein R^{1C} is amino can be prepared from an acetophenone derivative of formula 4 according to Group 4-scheme 2:

Group 4 - Scheme 2

(2, wherein R^{1C} is NH_2)

15

5

10

According to Group 4-scheme 2, 4'-hydroxyacetophenone (Aldrich Chemical Co., Milwaukee, WI,
USA) was reacted with thiourea and iodine according
to the method of R.M. Dodson and L.C. King, J. Amer.
Chem. Soc. 1945, 67, 2242 to give 4-(2-amino-4thiazolyl)phenol (5). Reaction of the latter
compound with 1,1-dimethylethyl 2-bromoacetate in
the presence of potassium carbonate gave 1,1dimethylethyl 2-{4-(2-amino-4-thiazolyl)phenoxy}acetate (6). Subsequent hydrolysis of the later
compound gave the thiazolylphenoxyacetic acid
derivative of formula 2 wherein R^{1C} is amino.

Again in turn, the thiazolylphenoxyacetic acid of formula 2 wherein R^{1C} is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino can be prepared according to Group 4-scheme 3.

- 207 -

Group 4 - Scheme 3

2[R^{1CC}=hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino]

wherein R^{1CC} is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino.

According to Group 4-scheme 3, the compound of formula 7, 4-(bromoacetyl)phenyl benzoate (Aldrich Chemical Co.) is reacted with an appropriate

thioamide or thiourea of formula $H_2N-C(S)-R^{1CC}$ wherein R1CC is as defined hereinbefore, according to the classical reaction described by R.H. Wiley et al., Organic Reactions 1951, 6, 369-373 for preparing thiazole compounds from thioamides or 5 thioureas and α -halocarbonyl compounds, to obtain the corresponding protected thiazolylphenol derivative of formula 8. Thereafter, acid hydrolysis of the latter derivative effects the removal of the benzoyl protective group to give the 10 corresponding thiazolylphenol of formula 9 which on reaction with 1,1-dimethylethyl 2-bromoacetate in the presence of potassium carbonate gives the 1,1dimethyl ester of formula 10. Subsequent hydrolysis of the latter ester yields the thiazolylphenoxy-15 acetic acid of formula 2 wherein R^1 is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino. The thiazolylphenoxyacetic acid of formula 2 wherein R^{1C} is amino can serve as an intermediate for transformation by standard methods 20 to thiazolylphenoxyacetic acids of formula 2 wherein R1C is lower alkanoylamino or lower alkoxycarbonyl.

The starting materials for the preceding processes are known, as noted hereinabove for compounds 4 and 7, or they can be prepared by standard methods.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled

- 209 -

30

in the art. In all such cases, the reaction can be successfully performed by conventional modification known to those skilled in the art, e.g. by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, or by modification illustrated in the examples herein.

Furthermore, if desired, the compound of Group 4formula 1c can be obtained in the form of a
therapeutically acceptable acid addition salt. Such
salts can be considered as biological equivalent of
the compounds of Group 4-formula 1c. Examples of
such salts are those formed with hydrochloric acid,
sulfuric acid, phosphoric acid, formic acid, acetic
acid or citric acid.

Antiherpes Activity

5

The antiviral activity of the compounds of Group 4formula 1c, or a therapeutically acceptable acid
addition salt thereof, can be demonstrated by
biochemical, microbiological and biological
procedures in the same manner as described
previously for the compounds of Group 1-formula 1.
Likewise the compounds of Group 4-formula 1c, or a
therapeutically acceptable acid addition salt
thereof, can be formulated and used as antiviral
agents in the same manner as described for the
compounds of Group 1-formula 1.

The following examples further illustrate this invention. Temperatures are given in degrees
Celsius. Solution percentages or ratios express a

volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance spectra were recorded on a Bruker 400 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. The concentrations for the optical rotations are expressed in grams of the compound per 100 mL of solution. Abbreviations or symbols used in the examples are as defined hereinbefore.

10

5

GROUP 4 EXAMPLES

Example 1

4-(2-Amino-4-thiazolyl)phenol

15

Thiourea (30.45 g, 400 mmol) and iodine (50.76 g, 200 mmol) were added to a solution of 4'hydroxyacetophenone (27.23 g, 200 mmol) in isopropanol (400 mL). The resulting mixture was 20 heated at reflux for 18 h, then diluted with H_2O and washed with Et₂O. The aqueous layer was rendered basic with a saturated aqueous solution of NaHCO3 and then extracted with EtOAc. The organic extract was washed with brine, dried (MgSO4) and 25 concentrated under reduced pressure to afford 15 g of an orange foam. The foam was purified by flash chromatography (SiO₂, 3:1, EtOAc:hexane) to afford the title compound (9.41 g, 25% yield) as a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d₆) δ 9.42 (s, 1H), 7.59 (d, J = 8.6 Hz, 2H), 6.93 (s, 2H), 6.73 30 (d, J = 8.6 Hz, 2H), 6.71 (s, 1H); MS (CI, NH₃) m/z193 (MH) + ...

- 211 -

Example 2

1,1-Dimethylethyl 2-{4-(2-amino-4-thiazolyl)phenoxy}acetate.

5

10

15

Potassium carbonate (3.80 g, 27.5 mmol) and tertbutyl 2-bromoacetate (4.04 mL, 25.0 mmol) were added to a solution of the product of example 1 (4.81 g, 25.0 mmol) in THF (125 mL). The resulting mixture was heated at reflux for 72 h and then diluted with EtOAc. The mixture was washed with a saturated aqueous solution of NaHCO3 and then brine, dried (MgSO4) and concentrated under reduced pressure. The crude yellow oil obtained was purified by flash chromatography (SiO2, 1:2 to 2:3 EtOAc:hexane) to afford 3.97 g (52% yield) of the title compound as a pale yellow solid: 1 H NMR (400 MHz, DMSO-d6) 6 O 7.71 (d, J= 8.2 Hz, 2H), 6.97 (s, 2H), 6.88 (d, J= 8.2 Hz, 2H), 6.83 (s, 1H), 4.65 (s, 2H), 1.43 (s, 9H); MS (FAB) $^{m/z}$ 307 (MH) +

Example 3

2-{4-(2-Amino-4-thiazolyl)phenoxy}acetic acid

25

30

20

Trifluoroacetic acid (50 mL) was added to a solution of the product of example 2 (3.81 g, 12.4 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at room temperature (20-22°) for 4 h, then concentrated under reduced pressure (coevaporated with CH_2Cl_2 and then Et_2O). The residue was triturated with Et_2O , then filtered and dried to afford 4.45 g (quantitative yield) of the title compound as a white solid: ¹H NMR (400 MHz, DMSO-d₆)

 δ 7.67 (d, J= 8.8 Hz, 2H), 6.97 (d, J= 8.8 Hz, 2H), 6.96 (s, 1H), 4.72 (s, 2H). The product was used without further purification for the following reaction (example 4).

5

10

Example 4

2-{4-(2-Amino-4-thiazoly1)phenoxy}-N-(cyclohexyl-methyl)acetamide (1c: R^{1C} = NH_2 , R^{2C} =H and R^{3C} =cyclohexylmethyl)

To a solution of the product of example 3 (358 mg, 1.0 mmol) in DMF (10 mL) were added successively cyclohexanemethylamine (130 μ L, 1.0 mmol), DIPEA (700 μ L, 4.0 mmol) and TBTU (321 mg, 1.0 mmol). The 15 resulting mixture was stirred at room temperature for 18 h and then diluted with EtOAc. The mixture was washed with a saturated aqueous solution of NaHCO3 and then brine, dried (MgSO4) and 20 concentrated under reduced pressure. The residue was purified by flash chromatography (SiO2, 4:1, EtOAc:hexane) to afford the title compound (300 mg, 87% yield) as a white solid: M.p. 145-147°; $^{1}\mathrm{H}$ NMR (400 MHz, DMSO-d₆) δ 8.00 (broad t, J = 6.0 Hz, 1H), 25 7.71 (d, J = 8.7 Hz, 2H), 6.98 (s, 2H), 6.94 (d, J =8.7 Hz, 2H), 6.84 (s, 1H), 4.48 (s, 2H), 2.97 (t, J = 6.4 Hz, 2H), 0.82-1.66 (m, 11H); MS (FAB) m/z 346 $(MH)^+$. Anal. Calcd for $C_{18}H_{23}N_3O_2S$: C, 62.58; H, 6.71; N, 12.16. Found: C, 62.48; H, 6.74; N, 30 12.17.

- 213 -

Example 5

In conjunction with the appropriate starting materials and intermediates, the procedures of Group 4-examples 1 to 4 can be used to prepare other compounds of Group 4-formula 1c. Examples of compounds thus prepared are listed in Table 1 and 2 of Group 4-example 5, together with mass spectrum data for the individual compounds and the results obtained from three assays demonstrating antiherpes activity. The assays are as described hereinbefore.

		TABLE 1				-		_
	Compound of structure:	of formula 1c having the :						
		OCH ₂ C(0) NR ^{2C} R ^{3C}						
ыZ		(1c)						
H # >	wherein R ^{1C} is designated as	1C is NH2 and R^{2C} and R^{3C} are 1 as follows:						
No	R2C	R³C	FAB/MS	HSV-1	HSV-1	ELISA	PRA	
			(m/z)	IC ₅₀	EC50	EC50	EC50	
			(um)	(µm)	(Mt)	(Mtd)	(MH)	
1	H	PhCH ₂	340	35	6.5	9.0	12	
2	Ħ		346	8.4	2:0	1.2	35	
		Z.,,						
3	H	PhCH ₂ CH ₂	354	>50	9.6	6.0	45	
4	PhCH ₂	PhCH ₂	430	17	2.8	4.0	13*	
ιΩ	Ħ	N CH ₂	341	48	10.6	09	>94	
		>						
9	Me	PhCH ₂	354	12	4.7	4.0	3.8	,
				7	7		;	_

- 215 -

TABLE 1	7AB/MS HSV-1 HSV-1 CMV (m/z) IC50 EC50 EC50	15 0 0 4	CH ₂ 341 16	CH ₂ 341 65 >18*	CH ₂ 366 30 >19*	Ph ₂ CH 416 6.8	332 >50	346 26 >57
	y R2C	н	н	H	н	Н	н	Me
	Entry No	7	ω	6	10	11	12	13

- 216 -

		TABLE 1 (continued)	. •				
446	76-					ELISA	PRA
No No	K*C	R3C	FAB/MS	HSV-1	HSV-1	CMO	CMS
}			(m/z)	IC ₅₀	EC50	EC ₅₀	EC50
			· (una)	(Mrl)	(FII)	(MI)	(IIM)
14	н	(4-Me ₂ CPh)CH ₂	396	12 B			
15	מ			0.21			7333
	=	(4-FPn)CH ₂	358	35			>16*
16	Н	(4-MeOPh)CH,	370	48			*00.
17	Н	(3-FPh)CH,	358	13 5			2074
		,	325	77:77			>21*

Cytotoxic at this concentration

- 217 -

			TABLE	2					_
	Compound of structure:	formula 1c having the	aving the						
	,	CH20CH2C	$\sqrt{OCH_2C(0)NR^{2C}R^{3C}}$					· - · · · · · · · · · · · · · · · · · ·	
EL I	RICIN	(1c)							
z f	 S								
K >	wherein R ^{1C} , designated a	, R^{2C} and R^{3C} are as follows:	ıre						
No	R1C	R2C	R ^{3C}	FAB/MS	HSV-1	HSV-1	ELISA	PRA	
				(Z/W)	TC20	EC50	EC_{50}	EC50	
				/	(htm)	(Mrd)	(III)	(MIN)	
	Me ₃ COC(0)NH	PhCH ₂	PhCH ₂	530	>50			75	
2	MeC (0) MH	PhCH ₂	PhCH2	472	>50			1 2	
	NHMe	PhCH ₂	PhCH,	444	>50			1.5	
			, , , , , , , , , , , , , , , , , , ,					- -	

Cytotoxic at this concentration

Group 5: Thiazolylphenylethylamine Derivatives

According to another embodiement of this invention, the present application refers to Group 5

thiazolylphenylethylamine derivatives having antiherpes activity. The selective action of these compounds against these viruses, combined with a wide margin of safety, renders the compounds as desirable agents for combating herpes infections.

10

These thiazolylphenylethylamine derivatives can be characterized structurally by the presence of a {4-(4-thiazolyl)phenyl}ethylamine moiety. Compounds possesing such a moeity have been reported previously, for example:

15

- Y. Kawamatsu et al., Eur. J. Med. Chem.-Chimica Therapeutica, 1981, 16, 355;
- T. Nakao et al., Japanese patent application 63-060978, published September 1, 1986; Chem.

20 Abstr., **1989**, 110, 716, 135228r;

- J.A. Lowe, European patent application 279,598, published August 24, 1988;
- A.A. Nagel, European patent application 372,776, published June 13, 1990;
- J.A. Lowe et al., J. Med. Chem., **1991**, 34, 1860; and
 - Y. Katsura et al., European patent application 545,376, published June 9, 1993.

The present thiazolylphenylethylamine derivatives can be distinguished readily from the prior art compounds in that they possess different chemical structures and biological activities.

- 219 -

The Group 5 thiazolylphenylethylamine derivatives of this invention can also be represented by formula 1d

$$\mathbb{R}^{1D} \stackrel{\mathbb{N}}{\longrightarrow} \mathbb{N}$$

$$(1d)$$

5

wherein R^{1D} has the same meaning as R defined hereinbefore and R^{2D} and R^{3D} are as defined hereinbefore.

A preferred set of Group 5 compounds of this invention is represented by Group 5-formula 1d wherein

R^{1D} is hydrogen, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, (lower alkoxycarbonyl)amino, or di(lower alkoxycarbonyl)amino;

R^{2D} is hydrogen, lower alkyl, phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; (lower cycloalkyl)-(1-3C)alkyl, or (Het)-(1-3C)alkyl wherein Het is as defined hereinbefore;

25

20

R^{3D} is lower alkyl, lower alkyl monosubstituted, disubstituted or trisubstituted with a halo; phenyl unsubstituted, monosubstituted or disubstituted with a halo, hydroxy, lower alkoxy or lower alkyl;

phenyl-(1-3C) alkyl unsubstituted, monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; lower cycloalkyl, (lower cycloalkyl)-(1-3C) alkyl, Het wherein Het is as defined hereinbefore, (Het)-(1-3C) alkyl wherein Het is as defined hereinbefore; lower alkylamino, di(lower alkyl) amino or phenyl-(1-3C) alkylamino unsubstituted, monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; or a therapeutically acceptable acid addition salt thereof.

A more preferred set of Group 5 compounds are represented by Group 5-formula 1d wherein R^{1D} is amino, methylamino, dimethylamino, acetylamino, (1,1-dimethylethoxycarbonyl)amino or di(1,1-dimethylethoxycarbonyl)amino;

R^{2D} is hydrogen, methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, phenylmethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4-fluorophenyl)methyl, (4-methoxyphenyl)methyl, cyclophenyl)methyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclohexylethyl, 2-(4-morpholinyl)ethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl or 3-thienylmethyl;

R^{3D} is methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, trifluoromethyl, phenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-chloro-2-methoxy-

- 221 -

30

phenyl, phenylmethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methy, (3-fluorophenyl)methyl, (4-fluorophenyl)methyl, (4-methoxyphenyl) methyl, cyclopentyl, cyclohexyl, cyclo-5 pentylmethyl, cyclohexylmethyl, 2-cyclohexylethyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-thienyl, 3thienyl, 2-(4-morpholinyl)ethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4pyridinyl)ethyl, 2-thienylmethyl, 3-thienylmethyl, 10 methylamino, ethylamino, propylamino, butylamino, (2-methylpropyl)amino, (2,2-dimethylpropyl)amino, dimethylamino, diethylamino, dipropylamino, dibutylamino, di(2-methylpropyl)amino, {di(2,2-di-15 methylpropyl) }amino, (phenylmethyl)amino, (2-phenylethyl)amino, {(4-chlorophenyl)methyl}amino, {(2fluorophenyl) methyl amino, {(3-fluorophenyl) methyl}amino, {(4-fluorophenyl)methyl}amino, {(4methoxyphenyl)methyl)amino; or a therapeutically 20 acceptable acid addition salt thereof.

A most preferred set of Group 5 compounds are represented by Group 5-formula 1d wherein R^{1D} is amino;

25

 R^{2D} is hydrogen or phenylmethyl;

R^{3D} is phenyl, phenylmethyl, {(4-fluorophenyl)-methyl}amino, cyclohexyl or dibutylamino; or a therapeutically acceptable acid addition salt thereof.

Another most preferred set of Group 5 compounds are represented by Group 5-formula 1d wherein R^{1D} is

amino, (1,1-dimethylethoxycarbonyl)amino or di(1,1-dimethylethoxycarbonyl)amino;

R^{2D} is hydrogen or phenylmethyl; and

5

R^{3D} is 2,2-dimethylpropyl, trifluoromethyl, phenyl, phenylmethyl, 4-pyridinyl or dibutylamino; or a therapeutically acceptable acid addition salt thereof.

10

Included within the scope of this invention is a pharmaceutical composition comprising an antiherpes virally effective amount of a compound of Group 5 as defined herein, or a therapeutically acceptable acid addition salt thereof, and a pharmaceutically or veterinarily acceptable carrier.

20

15

Still another aspect of this invention involves a method for treating acyclovir-resistant herpes infections in a mammal which comprises administering to the mammal an anti-acyclovir-resistant herpes effective amount of a compound of Group 5 as defined herein, or a therapeutically acceptable acid addition salt thereof.

25

Process for preparing the compounds of Group 5

The compounds of Group 5 can be prepared by a variety of processes involving known methods.

Description of the methods are found in standard textbooks such as "Annual Reports In Organic Synthesis - 1994", P.M. Weintraub et al., Eds., Academic Press, Inc., San Diego, CA, USA, 1994 (and the preceding annual reports), "Vogel's Textbook of

- 223 -

Practical Organic Chemistry", B.S. Furniss et al., Eds., Longman Group Limited, Essex, UK, 1986, and "Comprehensive Organic Synthesis", B.M. Trost and I. Fleming, Eds., Pergamon Press, Oxford, UK, 1991, Volumes 1 to 8.

A general process to prepare compounds of Group 5-formula 1d can be represented by Group 5-scheme 1:

10 <u>Group 5 - Scheme</u> 1

5

15

20

According to Group 5-scheme 1, a 4-thiazolylphenyl derivative of formula 2, wherein R^{1D} is as defined herein, is coupled with a carboxylic acid derivative of formula 3, wherein R^{3DA} is lower alkyl, lower alkyl monosubstituted, disubstituted or trisubstituted with a halo; phenyl unsubstituted, monosubstituted or disubstituted with a halo, hydroxy, lower alkoxy or lower alkyl; phenyl(lower alkyl) unsubstituted, monosubstituted or

disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; lower cycloalkyl, (lower cycloalkyl)-(lower alkyl), Het wherein Het is as defined hereinbefore, or (Het)-(lower alkyl) wherein Het is as defined hereinbefore; to give the amide derivative of formula 4, which is a compound of Group 5-formula 1d.

Alternatively, the 4-thiazolylphenyl derivative of formula 2 is reacted with phenyl chloroformate in the presence of a base to give the carbamate derivative of formula 5. The carbamate derivative of formula 5 is reacted with an amine of formula 6, wherein R^{4D} is hydrogen or lower alkyl, and R^{5D} is lower alkyl or phenyl lower alkyl unsubstituted, monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; to give the ureido derivative of formula 7, which is also a compound of Group 5-formula 1d.

The coupling of the 4-thiazolylphenyl derivative of formula 2 and the carboxylic acid of formula 3 is effected by the classical dehydrative coupling of a free carboxyl of one reactant with the free amino group of the other reactant in the presence of a coupling agent to form a linking amide bond, as described hereinbefore.

The compounds of formula 4 or formula 7, albeit compounds of Group 5-formula 1d, can also serve as intermediates for further elaboration by standard methods (e.g., N-alkylation, acylation, carbamate formation, etc.) with the appropriate agent to give

- 225 -

5

25

other compounds of Group 5-formula 1d, as well as corresponding compounds of Group 5-formula 1d in which \mathbb{R}^{2D} is other than hydrogen.

A convenient and practical process to prepare the requisite 4-thiazolylphenyl derivative of formula 2 of Group 5-scheme 1 is illustrated by Group 5-scheme 2:

Group 5 - Scheme 2

$$\begin{array}{c}
 & \text{NH}_2 \\
 & \text{(9)} \\
\end{array}$$

$$H_3C$$

$$0$$

$$(10)$$

$$H_2C$$

$$0$$

$$(11)$$

$$H_2C$$

$$0$$

$$0$$

$$11)$$

10

15

5

According to Group 5-scheme 2, phenethylamine of formula 8 is protected with an amino protecting group (PG1) to give a corresponding amino protected derivative of formula 9. The amino protected derivative of formula 9 is then reacted with acetyl chloride in the prescence of AlCl₃ in an inert solvent to give the corresponding methyl ketone derivative of formula 10, which is then reacted with

 Br_2 , Cl_2 or I_2 to give the corresponding α haloketone derivative of formula 11 wherein X is Br. Cl or I. The α -haloketone derivative of formula 11 is reacted with a thioamide of the formula H2N-C(S)- R^{1DA} wherein R^{1DA} is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino according to the classical reaction described by R.H. Wiley et al, Organic Reactions, 1951, 6, 367-374 for preparing thiazole compounds from thioamides and α halocarbonyl compounds, to obtain the corresponding thiazolyl derivative of formula 12. If desired, the thiazolyl derivative of formula 12 can be converted by standard methods (e.g., N-alkylation, acylation, carbamate formation, etc.) with the appropriate agent to give the corresponding compound of formula 12 wherein R^{1DA} has the same meaning as R^{1D} as defined hereinbefore. Subsequent deprotection of the latter compound gives the 4-thiazolylpheny derivative of formula 2.

20

25

30

15

5

10

Examples of amino protective groups suitable for use in the above schemes include benzyloxycarbonyl, tert-butyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl or 2,2,2-trifluoro-acetamide.

Other starting materials for the preceding process are known or they can readily be prepared by standard methods from known startingmaterials. For example, phenethylamine (8) is available from the Aldrich Chemical Co., Milwaukee, WI, USA.

The chemical reactions described above are generally disclosed in terms of their broadest application to

- 227 -

the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, the reaction can be successfully performed by conventional modification known to those skilled in the art, e.g. by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, or by modification illustrated in the examples herein.

Furthermore, if desired, the compounds of Group 5formula 1d can be obtained in the form of a
therapeutically acceptable acid addition salt. Such
salts can be considered as biological equivalent of
the compounds of formula 1d. Examples of such salts
are those formed with hydrochloric acid, sulfuric
acid, phosphoric acid, formic acid, acetic acid or
citric acid.

Antiherpes Activity

The antiviral activity of the compounds of Group 5formula 1d, or their corresponding therapeutically
acceptable acid addition salts, can be demonstrated
in the same manner as described herein for the
compounds of Group 1-formula 1. Likewise, the
compounds of Group 5-formula 1d, or their
corresponding therapeutically acceptable acid
addition salts, can be formulated and employed as
antiviral agents in the same manner as described
herein for the compounds of Group 1-formula 1.

5

10

The following examples further illustrate this invention. Temperatures are given in degrees Celsius. Solution percentages or ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance spectra were recorded on a Bruker 400 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. The concentrations for the optical rotations are expressed in grams of the compound per 100 mL of solution. Abbreviations or symbols used in the examples are as defined hereinbefore.

GROUP 5 EXAMPLES

15

10

5

Example 1

N-{2-{4-(2-Amino-4-thiazolyl)phenyl}ethyl}-2,2,2-trifluoroacetamide

20

25

30

(a) N-(2-Phenylethyl)-2,2,2-trifluoroacetamide: To a solution of phenethylamine (20.0 g, 165 mmol) in CH_2Cl_2 (350 mL) at 0° was added dropwise (5 min) trifluoroacetic anhydride (36.4 g, 173 mmol). The reaction was exothermic for the addition of the first half of the reagent. Pyridine (14.4 g, 185 mmol) was then added (10 min). The reaction was allowed to warm to room temperature and was then stirred for 16 h. The solution was washed with aqueous 10% HCl (2 x 200 mL) and H_2O (50 mL), dried (MgSO₄) and concentrated under reduced pressure to give N-(2-phenylethyl)-2,2,2-trifluoroacetamide as a pale yellow solid (35.8 g, 100% yield): 1H NMR (DMSO-d₆) δ 9.48 (broad s, 1H), 7.30 (m, 2H), 7.22

- 229 -

WO 97/24343 PCT/US96/19131 - ·

> (m, 3H), 3.42 (broad q, J = 6.8 Hz, 2H), 2.81 (t, J= 7.3 Hz, 2H).

- N-{2-(4-Acetylphenyl)ethyl}-2,2,2-trifluoro-5 acetamide: $AlCl_3$ (12.2 g, 91.7 mmol) was added to an ice-cold solution of N-(2-phenylethyl)-2,2,2-trifluoroacetamide (20.0 g, 91.8 mmol), prepared in the preceding section (a), and acetyl chloride (21.6 g, 275 mmol) in CH_2Cl_2 (200 mL). The reaction mixture
- was heated at reflux for 5 h (additional amounts of 10 AlCl₃, 12.2 g, were added to the ice-cold mixture after 1 and 2 h). The reaction mixture was cooled and poured into a mixture of ice (300 g) and aqueous 12N HCl (50 mL). The resulting solution was
- extracted with CH_2Cl_2 (4 x 50 mL). 15 The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$, dried $(MgSO_4)$ and concentrated under reduced pressure. Recrystallization of the resulting residue (24.1 g) from
- 20 EtOAc:hexane (2:3) gave N-{2-(4-acetylphenyl)ethyl}-2,2,2-trifluoroacetamide (16.7 g, 70% yield): ¹H NMR $(DMSO-d_6)$ δ 9.48 (broad s, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 3.46 (t, J = 7.2 Hz, 2H), 2.89 (t, J = 7.2 Hz, 2H), 2.55 (s, 3H). 25

 $N-\{2-\{4-(2-Bromoacetyl)phenyl\}ethyl\}-2,2,2$ trifluoroacetamide: Bromine (3.08 g, 19.3 mmol) was added to a cold (-10°) solution of $N-\{2-(4-acetyl$ phenyl)ethyl}-2,2,2-trifluoroacetamide (5.00 g, 19.3 30 mmol), prepared in the preceding section (b), in glacial acetic acid (20 mL) and CH_2Cl_2 (20 mL). produced from KBr (200 mg, 1.68 mmol) and ${\rm H}_2{\rm SO}_4$ (1 mL) was passed into the solution in a stream of dry N_2 . The solution was allowed to warm to 0° and

stirred for 3 h. The cold solution was diluted with hexane (40 mL) and stirred vigorously at 0° for 1 h. The resulting crystals were filtered off then were washed with H_2O and air dried to give $N-\{2-\{4-(2-bromoacetyl)phenyl\}ethyl\}-2,2,2-trifluoroacetamide (5.53 g, 85% yield): <math>^1H$ NMR (DMSO- 1H) 1H NMR (DMSO-

10

15

20

25

30

5

(d) The title compound: A solution of $N-\{2-\{4-(2-1)\}\}$ bromoacetyl)phenyl}ethyl}-2,2,2,-trifluoroacetamide (1.00 g, 2.96 mmol), prepared in the preceding section (c), and thiourea (225 mg, 2.96 mmol) in isopropanol (30 mL) was heated at reflux for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of EtOAc and aqueous 10% HCl and the phases were separated. The aqueous layer was washed with EtOAc then rendered basic with solid K₂CO₃. The resulting mixture was extracted with EtOAc. The organic layer was dried (MgSO₄) and concentrated under reduced The residue was purified by flash chromatography (SiO₂, EtOAc:Hexane, 1:1) to give N-{2-{4-(2-amino-4-thiazoly1)pheny1}ethy1}-2,2,2trifluoroacetamide (240 mg, 26% yield): M.p. 180-182°; ¹H NMR (DMSO- d_6) δ 9.48 (broad t, J = 5.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.00 (broad s, 2H), 6.95 (s, 1H), 3.43 (broad q, J = 6.8 Hz, 2H), 2.80 (t, <math>J = 7.2 Hz, 2H); MS(FAB) m/z 316 (MH)+; Anal. Calcd for $C_{13}H_{12}F_3N_3OS$: C, 49.52; H, 3.84; N, 13.33; S, 10.17. Found: C, 49.69; H, 3.82; N, 13.36; S, 10.00.

- 231 -

Example 2

5

 $N-\{2-\{4-(2-Amino-4-thiazolyl)phenyl\}ethyl\}$ benzene-acetamide (ld: $R^{1D}=NH_2$, $R^{2D}=H$ and $R^{3D}=PhCH_2$)

- 4-{4-(2-Aminoethyl)phenyl}-2-thiazolamine: A solution of $N-\{2-\{4-(2-bromoacetyl)phenyl\}ethyl\}$ -10 2,2,2-trifluoroacetamide (5.55 g, 16.4 mmol), prepared in Example 1(b), and thiourea (1.25 g, 16.4 mmol) in isopropanol (60 mL) was heated at reflux for 1 h. The reaction mixture was concentrated under reduced pressure to give crude $N-\{2-\{4-(2-1)\}\}$ 15 amino-4-thiazolyl)phenyl}ethyl}-2,2,2-trifluoroacetamide hydrobromide (6.51 g, ~100% yield). A solution of the crude hydrobromide and aqueous 4N NaOH (14.3 mL, 57.4 mmol) in MeOH (70 mL) and $\rm H_{2}O$ 20 (10 mL) was heated at reflux for 20 min. solution was cooled, H_2O (30 mL) was added and the MeOH was carefully evaporated under reduced pressure while keeping the solution cool. The resulting suspension was cooled to 0°. The crystals obtained 25 by filtration were washed with cold H_2O then airdried to give 4-{4-(2-aminoethyl)phenyl}-2-thiazolamine (3.3 g, 92% yield): 1 H NMR (DMSO- d_{6}) δ 7.69 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 7.03(broad s, 2H), 6.92 (s, 1H), 2.76 (t, J = 7.1 Hz, 30 2H), 2.62 (t, J = 7.1 Hz, 2H).
 - (b) The title compound: TBTU (366 mg, 1.14 mmol) was added to an ice-cold solution of 4-{4-(2-aminoethyl)phenyl}-2-thiazolamine (250 mg, 1.14

mmol), prepared in the preceding section (a), phenylacetic acid (171 mg, 1.25 mmol) and DIPEA (162 mg, 1.25 mmol) in DMF (3 mL). The solution was stirred at room temperature for 3 h then left at 6° 5 for 40 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with aqueous saturated $NaHCO_3$ (3 x 30 mL). The aqueous layers were back extracted with EtOAc (30 mL). The combined organic extracts were dried (MgSO₄) then concentrated under 10 reduced pressure. The residue was purified by flash amino-4-thiazolyl)phenyl}ethyl}benzeneacetamide as colorless crystals (343 mg, 84% yield): M.p. 176-177°; ¹H NMR (DMSO-d₆) δ 8.07 (broad t, J = 5.1 Hz, 15 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.20-7.30 (m, 5H), 7.15 (d, J = 8.4 Hz, 2H), 7.00 (broad s, 2H), 6.93(s, 1H), 3.29 (broad q, J = 6.7 Hz, 2H), 2.80 (t, J)= 7.3 Hz, 2H); MS (FAB) m/z 338 (MH)+; Anal. Calcd for $C_{19}H_{19}N_3OS$: C, 67.63; H, 5.68; N, 12.45; S, 20 9.50. Found: C, 67.55; H, 5.73; N, 12.38; S, 9.30.

Example 3

- $N-\{2-\{4-(2-Amino-4-thiazolyl)phenyl\}ethyl\}-N',N'-$ 25 dibutylurea (1d: $R^{1D}=NH_2$, $R^{2D}=H$ and $R^{3D}=dibutylamino$)
- (a) Phenyl N-{2-{4-(Amino-4-thiazolyl)phenyl}-ethyl}carbamate: Phenyl chloroformate (714 mg, 4.56 mmol) was added to a solution of 4-{4-(2-30 aminoethyl)phenyl}-2-thiazolamine (1.00 g, 4.56 mmol) and DIPEA (589 mg, 4.56 mmol) in DMF (4 mL) at 0°. The solution was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with aqueous saturated

- 233 -

NaHCO₃ (3 x 30 mL). The aqueous layers were back extracted with EtOAc (30 mL). The combined organic extracts were dried MgSO₄) then concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂, EtOAc:Hexane, 3:2) to give phenyl N-{2-{4-(amino-4-thiazolyl)phenyl}ethyl}-carbamate (941 mg, 61% yield): 1 H NMR (DMSO- 1 d6) 1 O 7.82 (broad t, J = 5.7 Hz, 1H), 7.73 (d, J = 7.9 Hz, 2H), 7.36 (m, 2H), 7.21 (m, 3H), 7.06 (d, J = 7.9 Hz, 2H), 7.01 (broad s, 2H), 6.95 (s, 1H), ca. 3.29 (m, signal beneath H₂O signal), 2.80 (t, J = 7.3 Hz, 2H).

The title compound: A solution of phenyl N-(b) {2-{4-(amino-4-thiazolyl)phenyl}ethyl}carbamate (200 15 mg, 0.59 mmol), prepared in the preceding section (a), and dibutylamine (76.0 mg, 0.59 mmol) in DMSO (1 mL) was stirred at room temperature for 3 d. reaction mixture was diluted with EtOAc (30 mL) and 20 washed with aqueous saturated $NaHCO_3$ (2 x 30 mL). The aqueous layers were back extracted with EtOAc The combined organic extracts were dried $(MgSO_4)$ then concentrated under reduced pressure. The residue was purified by flash chromatography 25 (SiO₂, EtOAc:Hexane, 4:1) to give $N-\{2-\{4-(2-amino-1)\}\}$ 4-thiazolyl)phenyl}ethyl}-N',N'-dibutylurea (167 mg, 76% yield): M.p. 42-43°; ¹H NMR (DMSO- d_6) δ 7.70 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 6.99(broad s, 2H), 6.92 (s, 1H), 6.11 (broad t, J = 5.430 Hz, 1H), 3.23 (broad q, J = 6.6 Hz, 2H), 3.09 (t, J= 7.5 Hz, 4H), 2.70 (t, J = 7.3 Hz, 2H), 1.37 (m,4H), 1.21 (m, 4H), 0.86 (t, J = 7.3 Hz, 6H); MS (FAB) m/z 375 (MH) +.

5

10

Example 4

- 5 tert-Butyl N-{4-{4-{2-{((dibutylamino)carbonyl}amino}ethyl}phenyl}-2-thiazolyl}carbamate (1d:
 R^{1D}=tert-butoxycarbonylamino, R^{2D}=H and R^{3D}=dibutylamino)
- 10 A solution of N-{2-{4-(2-amino-4-thiazolyl)phenyl}ethyl $\}$ -N',N'-dibutylurea (293 mg, 0.78 mmol), prepared as in Example 3(b), DIPEA (101 mg, 0.78 mmol), DMAP (9.5 mg, 0.08 mmol) and di-tert-butyl dicarbonate (171 mg, 0.78 mmol) in DMF (2 mL) was 15 stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with aqueous saturated NaHCO₃ (2 \times 30 mL). aqueous layers were back extracted with EtOAc (30 The combined organic extracts were dried 20 (MgSO₄) then concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂, EtOAc:Hexane, 1:1) to give the title compound (183 mg, 49% yield): M.p. $70-75^{\circ}$; ¹H NMR (DMSO-d₆) δ 11.53 (broad s, 1H), 7.77 (d, J = 8.1 Hz, 2H), 7.4825 (s, 1H), 7.22 (d, J = 8.1 Hz, 2H), 6.12 (broad t. J= 5.5 Hz, 1H), 3.23 (broad q, J = 6.7 Hz, 2H), 3.09(t, J = 7.5 Hz, 4H), 2.72 (t, J = 7.2 Hz, 2H), 1.49(s, 9H), 1.37 (m, 4H), 1.21 (m, 4H), 0.85 (t, J =7.3 Hz, 6H); MS (FAB) m/z 475 (MH)+; Anal. calcd for 30 $C_{25}H_{38}N_4O_3S$: C, 63.26; H, 8.07; N, 11.80; S, 6.41.

Found: C, 62.95; H, 8.14; N, 11.80; S, 6.41.

- 235 -

Example 5

In conjunction with the appropriate starting
materials and intermediates, the procedures of Group
5-Examples 1 to 4 can be used to prepare other
compounds of Group 5-formula 1d. Examples of
compounds thus prepared are listed in Table 1 of
Group 5-Example 5, together with mass spectrum data
for the individual compounds and the results
obtained from assays demonstrating antiherpes
activity. The assays have been described
hereinbefore.

			TART.					
	4	formula 1d h	- 1					
	structure:		20					
K		(2 - X					
ZF	RIDN		<u>_</u> 0					
α >-	$S = \frac{J}{S}$ wherein R^{1D} , R^{2} as follows:	D and R ^{3D} a	$ m R^{2D}$ and $ m R^{3D}$ are designated					
No	R ^{1D}	R ^{2D}	R3D	FAB/MS	HSV-1	HSV-1	ELISA	PRA
				(MH) +	IC ₅₀	EC50	EC50	EC ₅₀
					(htm)	(µщ)	(MT)	(MII)
	NH2	Н	5-C1-2-MeOPh	388			5.9	*22.
7	NH_2	Ħ	Ph	324	11	4	2.0	*36*
3	$_{ m NH}_2$	Н	CF_3	316	>50			207
4	NH_2	Н	3-pyridinyl	325				50
5	NH_2	Н	ьрсн ₂	338	40			707
9	NH_2	н	Мезссн,	318	>50			2 6
7	NH_2	Н	Me ₃ CO	320	>50			27
8	NH ₂	Н	(4-FPh)CH2NH	371	45			>14*
								7.7

- 237 -

			TABLE 1					
Entry		_	Danit Tiron	3				
S N	R1D	R2D	R3D	FAB/MS	HSV-1	HSV-1	ELISA	PRA
				(m/z)	IC_{50}	EC50	EC ₅₀	ECSO
				(HW)	(Mrl)	(MII)	(MIN)	(MI)
6	NH_2	H	BunN	375	-			
10	NHS	האפ	1	,				16
;	7	בוורח2	er.	414	>50			12
-	NH ₂	PhCH ₂	<u></u>	420	9			12*
		····						1
12	NH,	DhCu	4					
;	7	2	4-pyriainyi	415	>50			7.7
113	NH2	$PhCH_2$	CF ₃	406	>50			5
14	$(Me_3COC(0))_2N$	Ħ	Чď	524	2 2			777
15	NH_2	PhCH,	PhcH.	420	062			6.7
16	Me ₂ COC(0)NH	H	Bit-N	975				7.0
17	W. (0) 000 -W		Duzin	4/5	2,20			1.9
	Me3COC (O) NH	PhCH ₂	Ph					49

Cytotoxic at this concentration

- 238 -

Claims:

1. A compound of the formula:

$$R \xrightarrow{N} I$$

$$S \xrightarrow{(G)}$$

5

wherein:

R is selected from the group consisting of hydrogen, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, (lower alkoxy-carbonyl)amino, di(lower alkoxycarbonyl)amino, ((lower alkylamino)carbonyl)amino and pyridinylamino; and Z is selected from the group consisting of:

15 (i) $NR^2-C(0)-Q-CH(R^3)-NR^4R^5$ wherein: R² is hydrogen or lower alkyl; Q is absent (i.e. a valance bond) or methylene; R³ is hydrogen, lower alkyl, phenyl(lower alkyl) or phenyl(lower alkyl) monosubstituted on the aromatic 20 portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; R4 is hydrogen, (1-8C)alkyl, {di(lower alkyl)amino}-(lower alkyl), phenyl(lower)alkyl, phenyl(lower)alkyl monosubstituted or disubstituted on the 25 aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; 1-indanyl, 2-indanyl, (lower cycloalkyl)-(lower alkyl), (Het)-(lower alkyl) wherein Het represents an unsubstituted, monosubstituted or disubstituted five or six membered, monovalent heterocyclic ring containing 30 one or two heteroatoms selected from the group

- 239 -

consisting of N, O or S, wherein each substituent is selected independently from the group consisting of halo, hydroxy, lower alkoxy and lower alkyl; or \mathbb{R}^3 and \mathbb{R}^4 together form a -(CH₂)_m-W- group wherein m is the integer 2 or 3 and W is methylene 5 or carbonyl, W being linked to the nitrogen atom bearing R⁵; and R⁵ is (1-8C)alkyl, phenyl(lower alkyl), phenyl-(lower alkyl) monosubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy 10 or lower alkyl; 1-indanyl, 2-indanyl, (lower cycloalkyl)-(lower alkyl), (Het)-(lower alkyl) wherein Het is as defined in this claim, phenylsulfonyl, 1or 2-naphthylsulphonyl, 5-(dimethylamino)-1naphthylsulfonyl, (lower alkylamino)sulfonyl, (di-15 (lower alkyl)amino}sulfonyl, (Het)-sulfonyl wherein Het is as defined in this claim, lower alkanoyl, (lower cycloalkyl)-(lower alkanoyl), {1-(lower alkyl)-(lower cycloalkyl)}carbonyl, (lower alkoxy)-20 carbonyl, phenyl-Y-(CH_2) $_n$ C(0) wherein Y is oxy (-0-) or thio (-S-) and n is 0, 1 or 2 when Y is oxy or n is 1 or 2 when Y is thio, monosubstituted or disubstituted phenyl-Y-(CH_2)₂C(O) wherein Y and n are as defined in this claim and the monosubstitution or 25 disubstitution occurs on the phenyl portion thereof with a substituent selected from the group consisting of halo, hydroxy, lower alkoxy and lower alkyl; phenyl(lower alkanoyl), phenyl(lower alkanoyl) monosubstituted or disubstituted on the phenyl portion thereof with a substituent selected 30 independently from the group consisting of azido, halo, hydroxy, lower alkoxy and lower alkyl; (Het)- $(CH_2)_nC(0)$ wherein Het and n are as defined in this claim, $(Het) - Y - (CH_2)_n C(O)$ wherein Het, Y and n are

as defined in this claim, 2-{(lower alkoxycarbonyl)amino)-1-oxoethyl, (lower alkylamino)carbonyl, {di(lower alkyl)amino}carbonyl or (lower alkylamino) thiocarbonyl;

5

(ii) NR^{2A}C(O)-A-NR^{3A}R^{4A} wherein: R^{2A} is hydrogen or lower alkyl; A is absent or carbonyl; R^{3A} is hydrogen, (1-8C)alkyl, 2-hydroxyethyl, 3-10 hydroxypropyl, (1-3C)alkyl monosubstituted with cyano, phenyl(lower alkyl), phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, di(lower alkyl)amino, lower alkoxy or lower alkyl; (lower 15 cycloalkyl)-(lower alkyl), or (Het)-(lower alkyl) wherein Het is as defined in this claim; and R^{4A} is (1-8C) alkyl, phenyl (lower alkyl), phenyl-(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, 20 di(lower alkyl)amino, lower alkoxy or lower alkyl; 1-indanyl, 2-indanyl, phenyl(lower alkyl) monosubstituted on the aliphatic portion thereof with a hydroxy; (lower cycloalkyl)-(lower alkyl), Het as defined in this claim, (Het)-(lower alkyl) 25 wherein Het is as defined in this claim or 3-1Hindolylmethyl: or R3A and R4A together with the nitrogen to which they are attached form an unsubstituted, monosubstituted or disubstituted five or six membered. 30 monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently from the group consisting of halo,

- 241 -

hydroxy, lower alkoxy and lower alkyl;

or \mathbb{R}^{3A} and \mathbb{R}^{4A} independently are:

wherein L is carbon, oxygen or nitrogen, with the proviso that when L is oxygen, one of R^{6A} or R^{7A} is absent; R^{5A} and R^{6A} are independently selected from the group defined for R^{3A} in this claim; and R^{7A} is independently selected from the group defined for R^{4A} in this claim;

- (iii) C(0)-NR^{2B}R^{3B} wherein:

 R^{2B} is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, phenyl(lower alkyl), phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy,
- lower alkyl or trifluoromethoxy; lower cycloalkyl, (lower cycloalkyl)-(lower alkyl), {1-hydroxy-(lower cycloalkyl)-(lower alkyl) or (Het)-(lower alkyl) wherein Het is as defined in this claim; 2-benzimidazolyl; and
- 20 R^{3B} is lower alkyl, phenyl(lower alkyl), phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy, lower alkyl or trifluoromethoxy; 1-indanyl, 2-indanyl, lower
- cycloalkyl, (lower cycloalkyl)-(lower alkyl), {1hydroxy-(lower cycloalkyl)}-(lower alkyl) or (Het)-(lower alkyl) wherein Het is as defined in this claim;

or R3B is:

5

wherein R4B is hydrogen, lower alkyl, phenyl(lower alkyl), phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy, lower alkyl or trifluoromethoxy; (lower cycloalkyl)-(lower alkyl) or (Het)-(lower alkyl) wherein Het is as defined in this claim; R^{5B} has the same significance as R^{2B} in this claim and R6B has the same significance as R3B in this claim; or R^{3B} is (CH₂)+NR^{5B}R^{6B} wherein t is 1 or 2 and R^{5B} and R^{6B} are as defined in this claim; or \mathbb{R}^{3B} is $\mathrm{CH}(\mathbb{R}^7)\,\mathrm{CH}_2\mathrm{OH}$ wherein \mathbb{R}^{7B} has the same significance as R4B in this claim; or R^{2B} and R^{3B} together with the nitrogen to which they are attached form an unsubstituted, monosubstituted or disubstituted five or six membered, monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently from the group consisting of halo, hydroxy, lower alkoxy, lower alkyl, phenyl(lower alkyl) and phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl;

25

30

5

10

15

20

(iv) OCH₂C(O)NR^{2C}R^{3C} wherein:

R^{2C} and R^{3C} are independently hydrogen, lower alkyl, phenyl, phenyl(lower alkyl), phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a substituent selected independently from the group consisting of halo,

- 243 -

hydroxy, lower alkoxy or lower alkyl; 1-indanyl, diphenylmethyl, lower cycloalkyl, (lower cycloalkyl)-(lower alkyl) or (Het)-(lower alkyl) wherein Het is as defined in this claim; with the provisos (a) that R^{2C} and R^{3C} cannot both be hydrogen, (b) that when R is hydrogen, methyl or dimethylamino then R^{2C} and R^{3C} cannot both be phenylmethyl, and (c) that when R is amino, then R^{2C} and R^{3C} cannot be the combination of hydrogen and 1,1-dimethylethyl or the combination of methyl and phenyl; and

- (v) CH₂CH₂N(R^{2D})-C(O)R^{3D} wherein R^{2D} is hydrogen, lower alkyl, phenyl(lower alkyl), phenyl(lower alkyl) monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; (lower cycloalkyl)-(lower alkyl), or (Het)-(lower alkyl) wherein Het is as defined in this claim; and
- R3D is lower alkyl, lower alkyl monosubstituted, disubstituted or trisubstituted with a halo; phenyl unsubstituted, monosubstituted or disubstituted with a halo, hydroxy, lower alkoxy or lower alkyl; phenyl(lower alkyl) unsubstituted, monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; lower cycloalkyl, (lower cycloalkyl)-(lower alkyl), Het wherein Het is as defined in this claim, (Het)-
- (lower alkyl) wherein Het is as defined in this claim; lower alkylamino, di(lower alkyl)amino, or phenyl(lower alkyl)amino unsubstituted, monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl;

or a therapeutically acceptable acid addition salt thereof.

- A method for inhibiting a herpes helicase primase comprising the step of contacting the herpes helicase-primase with a compound according to claim
 1.
- 3. A method for inhibiting replication of a herpesvirus comprising the step of contacting the herpes helicase-primase with a compound according to claim 1.

15

20

- 4. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically acceptable carrier and a compound according to claim 1.
- 5. The method according to claim 4, wherein the compound according to claim 1 is further characterized by an ability to inhibit replication of a herpesvirus in cell culture by at least about 50% at a concentration of less than about 5 µM.

30

6. The method according to claim 5, wherein the compound according to claim 1 is further characterized by an ability to inhibit replication

- 245 -

of a herpesvirus by at least about 50% at a concentration of less than about 2 μM .

7. The method according to claim 6, wherein the compound according to claim 1 is further characterized by an ability to inhibit replication of a herpesvirus by at least about 50% at a concentration of less than about 1 μM.

10

- 8. The method according to claim 7, wherein the compound according to claim 1 is further characterized by an ability to inhibit replication of a herpesvirus by at least about 50% at a concentration of less than about 500 nm.
- 9. The method according to claim 8, wherein the compound according to claim 1 is further characterized by an ability to inhibit replication of a herpesvirus by at least about 50% at a concentration of less than about 100 nM.

25

10. The method according to claim 5, wherein the compound according to claim 1 is further characterized by an ability to inhibit herpes helicase-primase mediated RNA primer biosynthesis.

30

11. The method according to claim 5, wherein the herpesvirus is HSV-1.

12. The method according to claim 5, wherein the herpesvirus in HSV-2.

5

- 13. The method according to claim 5, wherein the herpesvirus is HCMV.
- 10 14. The method according to claim 5, wherein the compound according to claim 1 is further characterized by an ability to bind to an allosteric effector site located on the UL5 or UL52 subunit of the HSV-1 helicase-primase.

15

20

- 15. The method according to claim 14, wherein the compound according to claim 1 is further characterized by an ability to bind to the A-B sequence of the UL52 subunit of the HSV-1 helicase-primase.
- 16. The compound according to claim 1, further characterized by an ability to inhibit replication of a herpesvirus by at least about 50% at a concentration of less than about 100 nm.
- 17. The compound according to claim 16, further characterized by an ability to inhibit replication of a herpesvirus by at least about 50% at a concentration of less than about 50 nM.

- 247 -

18. The compound according to claim 17, further characterized by an ability to inhibit replication of a herpesvirus by at least about 50% at a concentration of less than about 10 nM.

- 19. The compound according to claim 19 further characterized by an ability to inhibit replication of a herpesvirus by at least about 50% at a concentration of less than about 1 nM.
- 20. The compound according to claim 1, further characterized by an ability to bind to an allosteric effector site located on the UL5 or UL52 subunit of the HSV-1 helicase-primase.
- 21. The compound according to claim 20, further characterized by an ability to bind to the A-B sequence of the UL52 subunit of the HSV-1 helicase-primase.
- 22. A pharmaceutical composition comprising the compound according to claim 1 and a pharmaceutically acceptable carrier.
- 30 23. The pharmaceutical composition according to claim 22, wherein the composition is suitable for oral administration.

5

25

24. The pharmaceutical composition according to claim 22, wherein the composition is suitable for topical administration.

5

10

25. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of the pharmaceutical composition according to claim 22.

mammal
15 mammal
effect

26. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of the pharmaceutical composition according to claim 23.

20

27. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of the pharmaceutical composition according to claim 24.

25

30

- 28. A method for inhibiting a herpes helicaseprimase comprising the step of contacting the herpes helicase-primase with a non-nucleoside compound characterized by:
- (a) an ability to inhibit DNA-dependent NTPase activity of the herpes helicase-primase;

- 249 -

(b) an ability to stabilize the interaction between the herpes helicase-primase and a DNA substrate;

- (c) an inability to inhibit DNA-independent NTPase activity of the herpes helicase-primase;
- (d) an inability to bind directly to doublestranded DNA; and
- (e) an inability to inhibit the herpes origin binding protein helicase encoded by the UL9 gene of HSV-1.
- 29. A method for inhibiting replication of a herpes virus comprising the step of contacting the herpes helicase-primase with a non-nucleoside compound characterized by:
 - (a) an ability to inhibit DNA-dependent NTPase activity of the herpes helicase-primase;
- (b) an ability to stabilize the interaction between the herpes helicase-primase and a DNA substrate;
 - (c) an inability to inhibit DNA-independent NTPase activity of the herpes helicase-primase;
 - (d) an inability to bind directly to doublestranded DNA; and
 - (e) an inability to inhibit the herpes origin binding protein helicase encoded by the UL9 gene of HSV-1.

30

5

10

15

20

25

30. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition

comprising a therapeutically acceptable carrier and a non-nucleoside compound characterized by:

- (a) an ability to inhibit DNA-dependent NTPase activity of the herpes helicase-primase;
- (b) an ability to stabilize the interaction between the herpes helicase-primase and a DNA substrate:
- (c) an inability to inhibit DNA-independent NTPase activity of the herpes helicase-primase;
- (d) an inability to bind directly to double-stranded DNA; and
- (e) an inability to inhibit the herpes origin binding protein helicase encoded by the UL9 gene of HSV-1.

15

20

10

5

- 31. The method according to claim 30, wherein the non-nucleoside compound is further characterized by an ability to inhibit replication of a herpes virus in cell culture by at least about 50% at a concentration of less than about 5 µM.
- 32. The method according to claim 31, wherein the non-nucleoside compound is further characterized by an ability to inhibit replication of a herpes virus by at least about 50% at a concentration of less than about 2 µM.

30

33. The method according to claim 32, wherein the non-nucleoside compound is further characterized by an ability to inhibit replication of a herpes virus

- 251 -

by at least about 50% at a concentration of less than about 1 μM_{\odot}

5 34. The method according to claim 33, wherein the non-nucleoside compound is further characterized by an ability to inhibit replication of a herpes virus by at least about 50% at a concentration of less than about 500 nM.

10

15

- 35. The method according to claim 34, wherein the non-nucleoside compound is further characterized by an ability to inhibit replication of a herpes virus by at least about 50% at a concentration of less than about 100 nm.
- 36. The method according to claim 31, wherein the non-nucleoside compound is further characterized by an ability to inhibit herpes helicase-primase mediated RNA primer biosynthesis.
- 37. The method according to claim 31, wherein the herpes virus is HSV-1.
 - 38. The method according to claim 31, wherein the herpes virus in HSV-2.

30

39. The method according to claim 31, wherein the herpes virus is HCMV.

40. The method according to claim 31, wherein the non-nucleoside compound is further characterized by an ability to bind to an allosteric effector site located on the UL5 or UL52 subunit of the HSV-1 helicase-primase.

- 41. The method according to claim 40, wherein the non-nucleoside compound is further characterized by an ability to bind to the A-B sequence of the UL52 subunit of the HSV-1 helicase-primase.
- 15 42. A method for identifying a non-nucleoside herpes helicase-primase inhibitor comprising the non-sequential steps of:
 - (a) measuring the ability of the test compound to inhibit DNA-dependent NTPase activity of the herpes helicase-primase; and
 - (b) measuring the ability of the test compound to inhibit DNA-independent NTPase activity.
- 43. The method according to claim 42, further comprising the step of measuring the ability of the test compound to inhibit herpes helicase-primase mediated RNA primer biosynthesis.
- 30 44. The method according to claim 42, further comprising the step of measuring the ability of the test compound to stabilize the interaction between the herpes helicase-primase and a DNA substrate.

- 253 -

5

45. The method according to claim 42, further comprising the step of measuring the ability of the test compound to bind directly to double-stranded DNA.

- 46. A non-nucleoside herpes helicase-primase inhibitor identified by the method according to claim 42.
- 47. The inhibitor according to claim 46, wherein said inhibitor is a thiazolylphenyl derivative.

15

20

25

30

10

- 48. A non-nucleoside herpes helicase-primase inhibitor characterized by:
- (a) an ability to inhibit DNA-dependent NTPase activity of the herpes helicase-primase;
 - (b) an ability to stabilize the interaction between the herpes helicase-primase and a DNA substrate;
- (c) an ability to inhibit replication of a herpes virus in cell culture by at least about 50% at a concentration of less than about 500 nm;
 - (d) an inability to inhibit DNA-independent NTPase activity of the herpes helicase-primase;
- (e) an inability to bind directly to doublestranded DNA; and
 - (f) an inability to inhibit the herpes origin binding protein helicase encoded by the UL9 gene of HSV-1.

5

- 49. The inhibitor according to claim 48, further characterized by an ability to inhibit replication of a herpes virus by at least about 50% at a concentration of less than about 100 nM.
- 50. The inhibitor according to claim 49, further characterized by an ability to inhibit replication of a herpes virus by at least about 50% at a concentration of less than about 50 nM.
- 51. The inhibitor according to claim 50, further characterized by an ability to inhibit replication of a herpes virus by at least about 50% at a concentration of less than about 10 nM.
- 52. The inhibitor according to claim 51 wherein the non-nucleoside compound is characterized by an ability to inhibit replication of a herpes virus by at least about 50% at a concentration of less than about 1 nM.

25

30

- 53. The inhibitor according to claim 48, further characterized by an ability to bind to an allosteric effector site located on the UL5 or UL52 subunit of the HSV-1 helicase-primase.
- 54. The inhibitor according to claim 53, further characterized by an ability to bind to the A-B

- 255 -

sequence of the UL52 subunit of the HSV-1 helicase-primase.

- 55. A pharmaceutical composition comprising the non-nucleoside herpes helicase-primase inhibitor according to any one of claims 48-54 and a pharmaceutically acceptable carrier.
- 56. The pharmaceutical composition according to claim 55, wherein the composition is suitable for oral administration.
- 57. The pharmaceutical composition according to claim 55, wherein the composition is suitable for topical administration.
- 58. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of the pharmaceutical composition according to claim 55.

25

- 59. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of the pharmaceutical composition according to claim 56.
- 60. A method for treating herpes infection in a mammal comprising the step of administering to a

mammal in need of such treatment a therapeutically effective amount of the pharmaceutical composition according to claim 57.

5

61. A method of treating a herpes viral infection in a mammal comprising administering to the mammal an anti-herpes virally effective amount of a compound as defined in claim 1, or a therapeutically acceptable acid addition salt therof.

10

62. A compound of formula G of claim 1 represented by formula 1

15

wherein R1 is selected from the group consisting of hydrogen, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, (lower alkoxycarbonyl)amino and {(lower 20 alkylamino)carbonyl}amino; R2 is hydrogen, methyl or ethyl; Q is absent or methylene; R3 is hydrogen, lower alkyl, phenylmethyl or phenylmethyl substituted on the 4 position of the phenyl ring with halo, lower alkoxyl or lower alkyl; R4 is 25 hydrogen, (1-8C)alkyl, {di(lower alkyl)amino}-(lower alkyl), phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted on the aromatic portion thereof with halo, hydroxy, lower alkoxy or lower alkyl; 1indanyl, 2-indanyl, (lower cycloalkyl)-(lower alkyl)

- 257 -

or (Het)-lower alkyl wherein Het is as defined hereinbefore; or \mathbb{R}^3 and \mathbb{R}^4 together form a $\mathrm{CH_2CH_2-W-}$ group wherein W is as defined hereinbefore; and \mathbb{R}^5 is (1-8C)alkyl, lower cyclohexyl, 1-pyrrolidinyl-5 ethyl, phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted on the aromatic portion thereof with halo, hydroxy, lower alkoxy or lower alkyl; 1indanyl, 2-indanyl, (lower cycloalkyl)-(1-3C)alkyl, (Het)-(1-3C)alkyl wherein Het is as defined 10 hereinbefore, phenylsulfonyl, 5-(dimethylamino)-1naphthylsulfonyl, (lower alkylamino)sulfonyl, {di(lower alkyl)amino}sulfonyl, (Het)-sulfonyl wherein Het is as defined hereinbefore, lower alkanoyl, (lower cycloalkyl)-(lower alkanoyl), (1-15 methylcyclohexyl)carbonyl, (lower alkoxy)carbonyl, (phenylmethoxy)carbonyl, 2-phenoxyacetyl, 2phenoxyacetyl monosubstituted or disubstituted on the phenyl ring with a substituent selected independently from the group consisting of bromo, 20 chloro, fluoro, iodo, methoxy and methyl; phenyl-(1-3C)alkanoyl, phenyl-(1-3C)alkanoyl monosubstituted or disubstituted with a substituent selected independently from the group consisting of azido, bromo, chloro, fluoro, iodo, methoxy and methyl; 25 $(\text{Het}) - (\text{CH}_2)_n C(0)$ wherein Het and n are as defined hereinbefore, $(Het)-Y-(CH_2)_nC(O)$ wherein, Het, Y and n are as defined hereinbefore, 2-{(lower alkoxycarbonyl)amino}-1-oxoethyl, (lower alkylamino)carbonyl, {di(lower alkyl)amino}carbonyl or (lower alkylamino) thiocarbonyl; or a therapeutically 30 acceptable acid addition salt thereof.

A compound of formula 1 of claim 62 wherein R1 is hydrogen, amino, methyl, methylamino, dimethylamino, acetylamino, (1,1dimethylethoxycarbonyl)amino or {(1,1-5 dimethylethylamino) carbonyl amino; R2 is hydrogen or methyl; Q is absent or methylene; R3 is hydrogen, methyl or phenylmethyl; R4 is hydrogen, methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2dimethylpropyl, 1-propylbutyl, 2-(dimethylamino)-10 ethyl, phenylmethyl, 1(R)-phenylethyl, 1(S)phenylethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4fluorophenyl) methyl, (4-methoxyphenyl) methyl, (2methylphenyl) methyl, 1-indanyl, 2-indanyl, cyclo-15 pentylmethyl, cyclohexylmethyl, 1(S)-cyclohexylethyl, 2-cyclohexylethyl, 2-(4-morpholinyl)ethyl, 2pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl or 3thienylmethyl; and R^5 is methyl, ethyl, propyl, 20 butyl, 2,2-dimethylpropyl, 1-propylbutyl, cyclohexyl, 1-pyrrolidinylethyl, phenylmethyl, 1(R)phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, (4chlorophenyl) methyl, (2-fluorophenyl) methyl, (3-25 fluorophenyl)methyl, (4-fluorophenyl)methyl, (2hydroxyphenyl) methyl, 4-(methoxyphenyl) methyl, (2methylphenyl)methyl, 1-indanyl, 2-indanyl, cyclopentylmethyl, cyclohexyl-methyl, 2cyclohexylethyl, 2-(4-morpholinyl)ethyl, 2-30 pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-thienylmethyl, phenylsulfonyl, 5-(dimethylamino) -1-naphthylsulfonyl, (dimethylamino) sulfonyl, 4-morpholinylsulfonyl, acetyl, 2-methylpropionyl, 2,2-dimethylpropionyl, 3,3-dimethyl-

- 259 -

butyryl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, cyclopentylacetyl, cyclohexylacetyl, cycloheptylacetyl, (1-methylcyclohexyl)carbonyl, (1-methylethoxy)carbonyl, (1,1-5 dimethylethoxy)carbonyl, (2-methylpropoxy)carbonyl, (phenylmethoxy) carbonyl, (2-phenoxy) acetyl, 2-(4,6dimethylphenoxy)acetyl, benzoyl, phenylacetyl, (4azidophenyl)carbonyl, (2-fluorophenyl)carbonyl, (3fluorophenyl)carbonyl, (4-fluorophenyl)carbonyl, (2,6-dimethylphenyl)carbonyl, 4-(1-methylpiperidin-10 yl)carbonyl, 2-(4-imidazolyl)acetyl, 2-pyridinylcarbonyl, 3-pyridinylcarbonyl, 4-pyridinylcarbonyl, N-oxido-4-pyridinylcarbonyl, 2-pyridinylacetyl, 4pyridinylacetyl, 6-(2,4-dihydroxypyrimidinyl)carbon-15 yl, 2-pyrazinylcarbonyl, 2-thienylcarbonyl, 3thienylcarbonyl, 4-morpholinylcarbonyl, 4piperidinylcarbonyl, 2-(2-pyrimidinylthio)acetyl, 2-(4,6-dimethyl-2-pyrimidinylthio)acetyl, 4-{1-(1,1dimethylethoxy)piperidinyl}carbonyl, 2-{(1,1dimethylethoxycarbonyl)amino}-1-oxoethyl, (1,1-20 dimethylethylamino)carbonyl, (N, N-dibutylamino)carbonyl, {N-methyl-N-(1,1-dimethylethyl)amino}carbonyl, or (1,1-dimethylethylamino)thiocarbonyl; or ${\rm R}^3$ and ${\rm R}^4$ together form a ${\rm CH_2CH_2CH_2}$ group and ${\rm R}^5$ 25 is butyl, 2,2-dimethylpropyl, 1-propylbutyl, benzyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, acetyl, 2-methylpropionyl, 2,2-dimethylpropionyl, 3,3-dimethylbutyryl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, cyclopentylacetyl, cyclohexylacetyl, cycloheptylacetyl, (1-30 methylcyclohexyl)carbonyl, (1-methylethoxy)carbonyl, (1,1-dimethylethoxy)carbonyl, (2-methylpropoxy)carbonyl or benzoyl, or \mathbb{R}^3 and \mathbb{R}^4 together form a CH₂CH₂C(0) group (wherein C(0) is linked to the

5

adjoining nitrogen atom), and R^5 is butyl, phenylmethyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, cyclopentylmethyl, cyclohexylmethyl or 2-cyclohexylethyl; or a therapeutically acceptable acid addition salt thereof.

64. A compound of formula 1 of claim 63 wherein R1 is hydrogen, amino, methylamino or dimethylamino; R2 10 is hydrogen or methyl; Q is absent; R3 is hydrogen, methyl or phenylmethyl; R4 is methyl, phenylmethyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (4fluorophenyl)methyl, (4-methoxyphenyl)methyl, (2-15 methylphenyl)methyl, 2-pyridinylmethyl, 3pyridinylmethyl, 4-pyridinyl-methyl, 2-(2pyridinyl) ethyl or 2-thienylmethyl; and R⁵ is 2,2dimethylpropionyl, 3,3-dimethylbutyryl, cyclopentylcarbonyl, cyclohexylcarbonyl, cyclo-20 heptylcarbonyl, cyclopentylacetyl, cyclohexylacetyl, (1-methylcyclohexyl)carbonyl, (1,1-dimethylethoxy)carbonyl, (2-methylpropoxy)carbonyl, benzoyl, (4fluorophenyl) carbonyl, (2,6-dimethylphenyl) carbonyl, 2-pyridinylcarbonyl, 3-pyridinylcarbonyl, 4-25 pyridinylcarbonyl, 4-morpholinylcarbonyl or (1,1dimethylethylamino) carbonyl; and the carbon atom bearing the R3 group when R3 is methyl or phenylmethyl has the (R) or (S) configuration; or \mathbb{R}^3 and R^4 together form a $CH_2CH_2CH_2$ group and R^5 is 30 cyclohexylcarbonyl, and the carbon atom bearing R3 (i.e the carbon atom linked to the CH2CH2CH2 group) has the (S) or (R) configuration; or a therapeutically acceptable acid addition salt thereof.

- 261 -

A compound of formula 1 of claim 63 wherein \mathbb{R}^1 is amino, methylamino, dimethylamino, acetylamino, (1,1-dimethylethoxy)carbonylamino or {(1,1-5 dimethylethylamino) carbonyl}amino; R2 is hydrogen; Q is absent or methylene; R3 is hydrogen or phenylmethyl; R^4 is hydrogen, methyl, 2,2dimethylpropyl, phenylmethyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-methylphenyl)methyl, 1-indanyl, 2-10 indanyl, cyclohexylmethyl, 2-pyridinylmethyl, 3pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl or 2-thienylmethyl; and R^5 is methyl, phenylmethyl, (2-fluorophenyl)methyl, (4fluorophenyl)methyl, (2-hydroxyphenyl)methyl, 4-15 morpholinylsulfonyl, 2,2-dimethylpropionyl, 3,3dimethylbutyryl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, cyclopentylacetyl, cyclohexylacetyl, (1,1dimethylethoxy)carbonyl, (2-methylpropoxy)carbonyl, 20 (2-phenoxy) acetyl, 2-(2,6-dimethylphenoxy) acetyl, benzoyl, phenylacetyl, 2-pyridinylcarbonyl, 3pyridinylcarbonyl, 4-pyridinylcarbonyl, 2pyridinylacetyl, 4-morpholinylcarbonyl, 2-25 thienylcarbonyl, 2-thienylacetyl, {(1,1-dimethylethyl)amino}carbonyl, {(1,1-dimethylethyl)amino}thiocarbonyl or 2-(4,6-dimethyl-2pyrimidinylthio)acetyl; and the carbon atom bearing the \mathbb{R}^3 group when \mathbb{R}^3 is phenylmethyl has the (R) or (S) configuration; or \mathbb{R}^3 and \mathbb{R}^4 together form a 30 CH2CH2CH2 group and R5 is cyclohexylcarbonyl or benzoyl, and the carbon atom linked to the $\mathrm{CH_2CH_2CH_2}$ group has the (R) or (S) configuration; or \mathbb{R}^3 and \mathbb{R}^4 together form a $CH_2CH_2C(0)$ group (wherein C(0) is

5

linked to the adjoining nitrogen atom), and R^5 is phenylmethyl or cyclohexylmethyl, and the carbon linked to the terminal methylene of the $CH_2CH_2C(O)$ group has the (R) or (S) configuration; or a therapeutically acceptable acid addition salt thereof.

- 66. A compound of formula 1 of claim 62 selected from the group consisting of:
 - (i) a compound of formula 1 wherein \mathbb{R}^1 is amino, \mathbb{R}^2 and \mathbb{R}^3 each is hydrogen, Q is absent, and \mathbb{R}^4 and \mathbb{R}^5 are as defined by one of the following combinations:

Combinations of R ⁴ and R ⁵		
R ⁴	_R 5	
Н	PhCH ₂	
Н	PhCH ₂ CH ₂	
Н	PhCH ₂ CH ₂ CH ₂	
Н	(4-FPh)CH ₂	
H	(4-ClPh)CH ₂	
H	(4-MePh)CH2	
н	(4-MeOPh)- CH ₂	
Н	СН2	
Н	(3-FPh)CH ₂	
Н	Ph-(S)-CHMe	
н	Ph-(R)-CHMe	

	Combinations of R4 and R5		
	R4	R ⁵	
	Н	N CH ₂	
	H	S CH ₂	
	н	NCH ₂ CH ₂	
	PhCH ₂	Me	
-	PhCH ₂	PhCH ₂	
L	(2-FPh)CH ₂	(2-FPh)CH ₂	
L	(3-FPh)CH ₂	(3-FPh)CH ₂	
	Н	C(0)	
	н	N C(0)	
	н	C (0)	
	Me	C(0)	
	PhCH ₂	PhC(O)	
	PhCH ₂	(4F- Ph)C(O)	
	PhCH ₂	(2,6-Me ₂ - Ph)C(O)	

Combinations of R ⁴ and R ⁵	
R ⁴	_R 5
PhCH ₂	PhCH ₂ C(O)
PhCH ₂	N C (0)
PhCH ₂	N C (0)
PhCH ₂	C(0)
PhCH ₂	-0 N C (0)
PhCH ₂	N CH ₂ C(0)
PhCH ₂	S C (0)
PhCH ₂	N C(0)
PhCH ₂	C(0)
PhCH ₂	C (0)
PhCH ₂	C(0)

- 265 -

R ⁴	ations of and R ⁵ tinued		
R4	_R 5		
PhCH ₂	-c(o)		
PhCH ₂	-01 ₂ C(0)		
PhCH ₂	CH ₂ C (0)		
PhCH ₂	Boc-N -C(0)		
PhCH ₂	Me ₃ CC(0)		
PhCH ₂	Me ₃ CCH ₂ C(O)		
PhCH ₂	Me ₂ CHC(0)		
PhCH ₂	MeC(O)		
(4-C1Ph)CH ₂	C(0)		
(4-MeOPh) - CH ₂	_c(o)		
N CH ₂	c(o)		
N CH ₂	_c(o)		
N CH ₂			
CH ₂ CH ₂			

- 266 -

Combinations of R ⁴ and R ⁵ continued		
R4	_R 5	
S CH2	_c (o)	
Ph-(R)-CHMe	_c (0)	
Ph-(S)-CHMe	_c(0)	
oNCH ₂ CH ₂	_c(0)	
(4-ClPh)CH ₂	N	
N CH ₂	N	
	NC(0)	
Ph-(S)CHMe	NC(0)	
(4-FPh)CH ₂	PhC(0)	
	PhC (0)	
	Boc-N	

- 267 ~

SUBSTITUTE SHEET (RULE 26)

	- R⁴	nations of and R ⁵ ntinued	
	R4	R5	
	СН2	HN C (0
))
		N C (0)
(4-C	LPh) CH ₂	N3-(_)-C(0)
PhCH ₂	СН ₂	C(0)	
PhCH ₂	CH ₂	N C(0)	
PhCH ₂	CH ₂	-C(O)	1
(4-C1	Ph)CH ₂	_a42c(0)	,
(4-C1, IPh)C		N C (0)	
PhCH ₂		NH ₂ CH ₂ C(O)	7
PhCH ₂		Me ₃ COC(0)- NHCH ₂ C(0)	
			_

Combinations of R ⁴ and R ⁵ continued	
R ⁴	_R 5
мсн2	(4-FPhe)- C(O)
PhCH ₂	N3
сн ₂	CH ₂ C (0)
СН2	CH2C (O)
	PhCH ₂ C(O)
N_CH ₂	N3(O)
N CH ₂ CH ₂	
Me ₃ CCH ₂	
Me ₂ CHCH ₂	_c (o)
Pr ₂ CH	-c (o)

- 269 -

R4	continued		
R4	R5		
(4-FPh)CH ₂	-c(o)		
(4-FPh)CH ₂	N		
PhCH ₂	Me ₃ COC(0)		
PhCH ₂	Me ₂ CHCH ₂ O- C(O)		
PhCH ₂	MeOC(O)		
Ph-(R)-CHMe	Me ₃ COC(0)		
Ph-(S)-CHMe	Me ₃ COC(0)		
NCH ₂	Me ₃ COC(0)		
(4-ClPh)CH ₂	Me ₃ COC(0)		
PhCH ₂	Me ₃ CNHC(0)		
PhCH ₂	Me ₃ CNHC(S)		
PhCH ₂	Me ₃ CN (Me) - C(O)		
PhCH ₂	ONC (O)		
PhCH ₂	oNso2		
PhCH ₂	PhSO ₂		
PhCH ₂	S(O) ₂		
	- 144E2		

Combinations of R ⁴ and R ⁵ continued		
R ⁴	R ⁵	
N_CH ₂	S (O) ₂	
CH ₂	Me ₃ COC(O)	
CH ₂ CH ₂	Me ₃ COC(O)	
(2-MePh)- CH ₂	NC(0)	
Сн2сн2		
PhCH ₂	Et ₂ CHC(0)	
Ph-(S)-CHMe	Me ₃ CNHC(O)	
PhCH ₂	Me ₂ NSO ₂	
СН2	0 N $-so_2$	
(S)-CHMe	Me3COC(O)	
PhCH ₂	PhCH ₂ OC (O)	
Me ₂ CHCH ₂	PhCH ₂ OC(O)	
Pr ₂ CH	Me ₃ COC(0)	

Combination		
Combination of R ⁴ and R ⁵ continued		
R4	_R 5	
Me ₂ CHCH ₂	Me ₃ COC(O)	
PhCH ₂	CH ₂ C(O)	
PhCH ₂	CH ₂ C(O)	
PhCH ₂	sC(0)	
PhCH ₂	S CH ₂ C(O)	
PhCH ₂	SCH ₂ C(O)	
(2-FPh)CH ₂	C(O)	
PhCH ₂	H ₂ N CH ₂ C(O)	
PhCH ₂	OCH ₂ C(O)	

	ion of R ⁴ and R ⁵ continued
R ⁴	_R 5
PhCH ₂	OCH ₂ C(O)
PhCH ₂	Me N SCH ₂ C(O)
PhCH ₂	Me N C(O)
(4-FPh)CH ₂	CH ₂ C(O)
PhCH ₂ CH ₂	C(O)
(3-FPh)CH ₂	CH ₂ C(O)
(2-MePh)CH ₂	CH ₂ C(O)
(2-MePh)CH ₂	s (0)
(2-MePh)CH ₂	Me OCH₂C(O) Me

- 273 -

	Combin	astion of p/	
	<u>L</u>	nation of R ⁴ and R ⁵ continued	
	R ⁴	R5	
	(2-MePh)CH	Me	_
	1.		
		l N	
		Me N SCH C(O)	
		Me N SCH ₂ C(O)	
		S CH2C(O)	
	(2-MePh)CH ₂		
			_
	(2 15-74) 00-	S CH₂C(O)	
	(2-MePh)CH ₂		i
		S C(O)	
	(2-MePh)CH ₂	S	i
ŀ			_
		N ← C(O)	ı
	Ph-(S)-CHMe		1
t	Ph- (S)-CHMe		4
	II-(S)-CHMe	Ň	1
			I
\perp		CH₂C(O)	
1	Ph-(R)-CHMe	N.	1
			ı
1		CH ₂ C(O)	
1	h-(R)-CHMe	2 (-)	-
1	(IV) -CIME	N 1	
		\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	
\vdash		~ `C(O)	
L			
Ι`	CH ₂	Me—N —C(O)	
-			
١,		N	
١ ١	CH ₂		
		CH ₂ C(O)	
1	Me ₂ NCH ₂ CH ₂		
	ł	C(O)	
	 L_	0(0)	

- 274 -

Combination of R ⁴ and R ⁵ continued		
R ⁴	R ⁴ R ⁵	
Pr ₂ CH	PhCH ₂ OC (O)	
Me ₂ CCH ₂	Me ₃ COC(O)	
PhCH ₂	PhCH ₂ NHS(O) ₂	

(ii) a compound of formula 1 wherein R^1 is amino, R^2 and R^3 each is H, and Q, R^4 and R^5 are as defined by one of the following combinations:

•

Combinations of Q, \mathbb{R}^4 and \mathbb{R}^5		
Q	R ⁴	R ⁵
CH ₂	H	PhCH ₂
CH ₂	PhCH ₂	PhCH ₂
сн2	PhCH ₂	PhC (0)
CH ₂	H	(3-FPh)CH ₂
CH ₂	(3-FPh) CH ₂	PhC (0)
CH ₂	PhCH ₂	N C (0)
СН2	PhCH ₂	N C (0)
сн2	PhCH ₂	
СH ₂	н	CH ₂ CH ₂

	Combination			
	0	Combinations o		
- }	Q		R5	
	CH ₂	H	CH ₂ CH ₂	
	СН2	CH ₂ CH ₂	N C (0)	
	Сн ₂	CH ₂ CH CH ₂	N C(0)	
	CH ₂	CH _{CH2}	Me3COC(O)	
C	сн ₂	CH ₂ CH ₂	Me ₃ COC(O)	
2	H ₂	PhCH ₂	Me ₃ COC(O)	
C	Н2	PhCH ₂	PhCH ₂ OC(O)	
L	H ₂	PhCH ₂	CH ₂	
C	H ₂	Ph-(S)-CHMe	Me3COC(O)	
C	H ₂	PhCH ₂	Ph-(S)-CHMe	
C	H ₂	н	Ph-(S)-CHMe	
	H ₂	CH ₂	Me ₃ COC(O)	
CI		н	CH ₂	
CI	12	Н	Pr ₂ CH	

- 276 -

С	ombinations of	Q , R^4 and R^5
Q	R ⁴	R ⁵
сн2	CH ₂	N—————————————————————————————————————
CH ₂	Н	Ph-(R)-CHMe
СH ₂	PhCH ₂	CH ₂
СH ₂	PhCH ₂	N-CH ₂ CH ₂
CH ₂	Ph-(S)-CHMe	Me
сн ₂	PhCH ₂	N CH ₂
сн ₂	PhCH ₂	CH ₂

(iii) a compound of formula 1 wherein \mathbb{R}^3 is hydrogen, Q is absent and \mathbb{R}^1 , \mathbb{R}^2 , \mathbb{R}^4 and \mathbb{R}^5 are as defined by one of the following combinations:

Combinations of \mathbb{R}^1 , \mathbb{R}^2 , \mathbb{R}^4 and \mathbb{R}^5			
R ¹	R ²	R ⁴	R ⁵
NH ₂	Ме	PhCH ₂	—c(0)
NH ₂	Me	PhCH ₂	NC(0)
NH ₂	Me	H	PhCH ₂
Me	н	PhCH ₂	

- 277 -

C	Combinations of all of				
	Combinations of R^1 , R^2 , R^4 and R^5				
R ¹	R ²	2 R4	R ⁵		
Н	н	PhCH ₂			
NHMe	H	PhCH ₂	PhC(O)		
NHMe	H	H	PhCH ₂		
NHMe	н	PhCH ₂			
NHMe	н	CH2	N C (0)		
NHMe	Н	PhCH ₂	Me ₃ COC(0)		
NMe ₂	Н	PhCH ₂	PhC(O)		
NMe ₂	H	Н	PhCH ₂		
NMe ₂	н	н	CH ₂		
NMe ₂	н	PhCH ₂	NC(0)		
NMe ₂	Н	PhCH ₂	N C (0)		
NMe ₂	H	PhCH ₂	Me ₃ COC(O)		
NMe ₂	н	CH ₂	Me ₃ COC(O)		
Me- C(O)NH	Н	PhCH ₂	CH ₃ C(O)		
Me- C(O)NH	H	PhCH ₂	NC(0)		
Me ₂ CH	н	PhCH ₂	PhC(O)		

- 278 -

Combinations of R^1 , R^2 , R^4 and R^5			
R ^l	R ²	R ⁴	R ⁵
Me ₃ CO-C(O)NH	н	PhCH ₂	Me N SCH ₂ C(O)
Me ₃ CO-C(O)NH	Н	Ph-(R)-CHMe	
Me ₃ CO-C(O)NH	H	Ph-(R)-CHMe	CH₂C(O)
Me ₃ CO-C(O)NH	н	Ph-(R)-CHMe	C(O)
Me ₃ CO-C(O)NH	н	Ph-(S)-CHMe	CH ₂ C(O)
Me-C(0)NH	н	Ph- (R)-CHMe	

(iv) a compound of formula 1 wherein R² and R³ each are hydrogen, Q is CH₂ and R¹, R⁴ and R⁵ are as defined by one of the following combinations:

Combinations of \mathbb{R}^1 , \mathbb{R}^4 and \mathbb{R}^5		
R1	R4	_R 5
Me3COC(O)NH	PhCH ₂	PhCH ₂
Me ₃ CNHC(0)NH	PhCH ₂	PhCH ₂

(v) a compound of formula 1 wherein \mathbb{R}^1 is amino, \mathbb{R}^2 is hydrogen, Q is absent and \mathbb{R}^3 , \mathbb{R}^4 and \mathbb{R}^5 are as defined by one of the following combinations:

Combinations			
Combinations of R ³ , R ⁴ and R ⁵ continued			
R ³	R ⁴	R ⁵	
(S)-PhCH ₂	н		
(R)-PhCH ₂	Н		
(S)-PhCH ₂	Н	Me ₃ COC(0)	
(R)-PhCH ₂	H	Me ₃ COC(0)	
(S)-PhCH ₂	Ме	C(0)	
(S)-PhCH ₂	н	PhCH ₂	
(R)-PhCH ₂	Н	PhCH ₂	
(S)-PhCH ₂	н	Me	
(R)-PhCH ₂	PhCH ₂	C(0)	
(S) -PhCH ₂	Me	Me ₃ COC(O)	
(S)-PhCH ₂	PhCH ₂		
(<i>S</i>) -Me	Н	PhCH ₂	
(R)-Me	H	PhCH ₂	

G = 1 : 4 : 5 = 2 = 4 : 3 = 5				
L	Combinations of \mathbb{R}^3 , \mathbb{R}^4 and \mathbb{R}^5			
R ³	R ⁴	R ⁵		
(<i>S</i>) -Me	PhCH ₂	C(0)		
(R)-Me	PhCH ₂			
(<i>S</i>) -Me	PhCH ₂	Me3COC(O)		
(R)-Me	PhCH ₂	Me ₃ COC(0)		
(R)-PhCH ₂	н	Me		
(S)-PhCH ₂	PhCH ₂	C(O)		
(R)-PhCH ₂	PhCH ₂	C(O)		
(S)-PhCH ₂	H	Me ₃ CCH ₂ C(0)		
(S)-PhCH ₂	H	Me ₃ CC (0)		
(S)-PhCH ₂	Н	MeC(O)		
(S)-PhCH ₂	H	Me ₂ CHOC(0)		
(S)-PhCH ₂	Me	Me ₃ COC(0)		
(S)-PhCH ₂	н	PhCH ₂ OC (O)		
(S) CH ₂	H	Me ₃ COC(O)		
(S)-PhCH ₂	Н	ON-S(O) ₂		
(S)(N-)-CH ₂	н	Me ₃ COC(O)		

and (vi) a compound of formula 1 having the structure

- 281 -

wherein the configuration of the asymmetric carbon atom linked (designated with an asterisk) to the $-(CH_2)_2$ W- group is indicated as follows, and W and R^5 as defined by one of the following combinations:

Combination of W and R ⁵				
	and configuration of			
a	asymmetric carbon atom			
W	R5	Configuration		
C(0)	PhCH ₂	R		
C(0)	PhCH ₂	S		
C (O)		R		
CH ₂	Me ₃ COC(0)	S		
CH ₂	PhC(O)	S		
CH ₂		S		
CH ₂	PhCH ₂	s		
CH ₂	Me ₃ COC(O)	R		
CH ₂	PhC (0)	R		
CH ₂		R		

10

67. A compound of formula G of claim 1 having the formula 1a:

5 wherein R^{1A} is selected from the group consisting of hydrogen, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino, (lower alkoxycarbonyl)amino, {(lower alkylamino)carbonyl}amino and 2-,3- or 4pyridinylamino; R2A is hydrogen, methyl or ethyl; A 10 is absent or carbonyl; R3A is hydrogen, (1-8C)alkyl, 2-hydroxyethyl, 3-hydroxypropyl, (1-3C)alkyl monosubstituted with cyano, phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted or disubstituted on the aromatic portion thereof with halo, hydroxy, 15 di(lower alkyl)amino, lower alkoxy or lower alkyl; (lower cycloalkyl) - (lower alkyl) or (Het) - (lower alkyl) wherein Het is as defined in claim 1; and R4A is (1-8C)alkyl, phenyl-(1-3C)alkyl, phenyl-(1-20 3C) alkyl monosubstituted or disubstituted on the aromatic portion thereof with halo, hydroxy, di(lower alkyl)amino, lower alkoxy or lower alkyl; 1-indanyl, 2-indanyl, 1-(hydroxymethyl)-2phenylethyl, (lower cycloalkyl)-(1-3C)alkyl, Het as 25 defined hereinbefore, (Het)-(1-3C)alkyl wherein Het

- 283 -

is as defined in claim 1 or 3-1H-indolylethyl; or

R4A is:

wherein L is oxygen or nitrogen, with the proviso that when L is oxygen, one of R^{6A} or R^{7A} is absent; R^{5A} and R^{6A} are independently selected from the group defined for R^{3A} herein; and R^{7A} is independently selected from the group defined for R^{4A} herein; or R^{3A} and R^{4A} together with the nitrogen to which they are attached form an unsubstituted, monosubstituted or disubstituted five or six membered, monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently from the group consisting of halo, hydroxy, lower alkoxy and lower alkyl; or a therapeutically acceptable acid addition salt thereof.

5

10

15

07217/38 · ·

A compound of formula 1a of claim 67 wherein RlA is hydrogen, amino, methyl, methylamino, butylamino, dimethylamino, acetylamino, (1,1-20 dimethylethoxycarbonyl)amino, 2-pyridinylamino or 3pyridinylamino; R^{2A} is hydrogen or methyl; A is absent or carbonyl; R3A is hydrogen, methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 25 1-propylbutyl, 2-hydroxyethyl, cyanomethyl, phenylmethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl) methyl, (3-fluorophenyl) methyl, (4fluorophenyl)methyl, (4-(dimethylamino)phenyl)methyl, (4-methoxyphenyl)methyl, (2-methyl-30 phenyl)methyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclohexylethyl, 2-(4-morpholinyl)ethyl, 2-

pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl or 3-thienylmethyl; and R^{4A} is 1,1-dimethylethyl, butyl, 2,2-5 dimethylpropyl, 1-propylbutyl, phenylmethyl, 1(R)phenylethyl, 1(S)-phenylethyl, 2-phenylethyl, (4chlorophenyl) methyl, (2-fluorophenyl) methyl, (3fluorophenyl)methyl, (4-fluorophenyl)methyl, (methoxyphenyl)methyl, {4-(dimethylamino)phenyl}methyl, (2-methylphenyl)methyl, 1-indanyl, 2-10 indanyl, (S or R)-1-(hydroxymethyl)-2-phenylethyl, cyclopentylmethyl, cyclohexylmethyl, 1(S)cyclohexylethyl, 1(R)-cyclohexylethyl, cyclohexylethyl, 1-piperidinyl, 2-(4morpholinyl) ethyl, 2-pyridinylmethyl, 3-pyridinyl-15 methyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2thienylmethyl, 3-(1H-imidazol-1-yl)propyl or 3-1Hindolylethyl; or 20 R4A is:

$$\begin{array}{ccc} & & & & \\ & & & \\ \text{HC-C-L} & & \\ & & & \\ \text{R}^{5\text{A}} & & & \\ \end{array} \\ \text{R}^{7\text{A}}$$

wherein L oxygen or nitrogen, with the proviso that when L is oxygen, one of R^{6A} or R^{7A} is absent; R^{5A} and R^{6A} are independently selected from the group defined for R^{3A} herein; and R^{7A} is independently selected from the group defined for R^{4A} herein; or R^{3A} and R^{4A} together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino or thiomorpholino; or a therapeutically acceptable acid addition salt thereof.

- 285 -

25

69. A compound of formula 1a of claim 68 wherein R^{1A} is amino, methylamino, dimethylamino or (1,1-dimethylethoxycarbonyl)amino; R^{2A} is hydrogen; A is absent; R^{3A} is hydrogen, methyl or butyl; and R^{4A} is 1,1-dimethylethyl, butyl, 1-propylbutyl, phenylmethyl, 2-phenylethyl, 4-fluorophenylmethyl, 1-piperidinyl, 2-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 4-pyridinylmethyl, 3-(1H-imidazol-1-yl)-propyl, or

10 R4A is:

5

15

wherein L is nitrogen, R^{5A} is phenylmethyl, R^{6A} is methyl and R^{7A} is 2-(2-pyridinyl)ethyl, or L is oxygen, R^{5A} is phenylmethyl, R^{6A} is absent and R^{7A} is 1,1-dimethylethyl; or a therapeutically acceptable acid addition salt thereof.

70. A compound of formula 1a of claim 68 wherein R^{1A} is amino, methylamino, butylamino, dimethylamino, (1,1-dimethylethoxycarbonyl)amino, 2-pyridinylamino or 3-pyridinylamino; R^{2A} is hydrogen; A is absent; R^{3A} is hydrogen, methyl, ethyl, butyl, 2-hydroxyethyl, cyanomethyl or phenylmethyl; and R^{4A} is butyl, phenylmethyl or 2-(4-pyridinyl)ethyl; or a therpaeutically acceptable acid addition salt therof.

71. A compound of formula 1a of claim 68 wherein R^{1A} is amino, R^{2A} is hydrogen, A is carbonyl, R^{3A} is butyl or phenylmethyl, and R^{4A} is butyl or

5

phenylmethyl, or a therapeutically acceptable acid addition salt therof.

- 72. A compound as defined in claim 67 selected from the group consisting of:
- (i) a compound of formula 1a wherein A is absent, R^{2A} is hydrogen, R^{1A} , R^{3A} and R^{4A} are as defined by one of the following combinations:

Combination of R ^{1A} , R ^{3A} and R ^{4A}		
R ^{1A}	_R 3A	R ⁴ A
NH ₂	Bu	Bu
NH ₂	H	Bu
NH ₂	н	CH ₂ N
NH ₂	CH ₃	CH ₂
NH ₂	н	CH ₂
NH ₂	н	CH ₂
NH ₂	H	(4-FPh)CH ₂
NH ₂	н	HC CH3 CH3

Combination of	of RIA	R^{3A} and R^{4A} (continued)
R ¹ A	R3A	R4A
NH ₂	Н	HC CH ₃
NH ₂	H	H ₂ C N N
NH ₂	н	HC CH3
NH ₂	Н	CH ₃ CH ₃
NH ₂	Н	CH ₂
Me3COC(O)NH	Ме	CH ₂
Me3COC(O)NH	Bu	Bu
NH ₂	Н	(PhCH ₂) ₂ NCH ₂ CH ₂
NH ₂	Н	HC≡CCH ₂
NH ₂	н	□ N S

Combinatio	n of RIA, R3	A and R ^{4A} (continued)
R1A	R3A	R4A
NH ₂	Н	CH ₂ CH ₂
NH ₂	Н	PhCH ₂
NH ₂	Н	(4-ClPh)CH ₂
NH ₂	н	(3-FPh)CH ₂
NH ₂	Ħ	(2-FPh)CH ₂
NH ₂	Н	(4-FPh)CH ₂ CH ₂
NH ₂	Н	(4-Me ₂ NPh)CH ₂
NH ₂	Н	Ph-(S)-CHMe
NH ₂	н	
NH ₂	Н	(S) - (PhCH2) CHCH2OH
Me ₃ COC(O)NH	Ме	CH ₂ CH ₂
Me ₃ COC(0)NH	Me	Bu
Me ₃ COC(0)NH	Et	Bu
Me ₃ COC(0)NH	носн ₂ сн ₂	Bu
Me ₃ COC(0)NH	NC-CH ₂	Bu
BuNH	Bu	Bu
NH	Bu	Bu
NH	Bu	Bu

- 289 -

(ii) and a compound of formula 1a wherein A is carbonyl, R^{1A} is amino, R^{2A} is hydrogen, and R^{3A} and R^{4A} are as defined by one of the following combinations:

Combination of	R ^{3A} and R ^{4A}
R3A	R4A
Butyl	Butyl
CH ₂ Ph	CH ₂ Ph

73. A compound of formula G of claim 1 having the formula 1b:

10

5

wherein R^{1B} is hydrogen, lower alkyl, amino, lower alkylamino, di(lower alkyl)amino, lower alkanoylamino or (lower alkoxycarbonyl)amino; R^{2B} is hydrogen, (1-8C)alkyl, lower alkenyl, lower alkynyl, phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy, lower alkyl or trifluoromethoxy; (lower cycloalkyl)-(1-3C)alkyl or (Het)-(1-3C)alkyl wherein Het is as defined in claim 1; 2-benzimidazolylmethyl; and R^{3B} is (1-8C)alkyl, phenyl-(1-3C)alkyl, phenyl-(1-

3C) alkyl monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy, lower alkyl or trifluoromethoxy; 1-indanyl, 2-indanyl, (lower cycloalkyl)-(1-3C)alkyl, {1-hydroxy(lower cycloalkyl)}-(1-3C)alkyl or (Het)-(1-3C)alkyl wherein Het is as defined in claim 1; or R^{3B} is:

- wherein R^{4B} and R^{5B} independently have the same 10 significance as defined for R2B in the last instance and R6B has the same significance as defined for R^{3B} in the last instance; or R^{3B} is CH2CH2NR5BR6B wherein R5B and R6Bare as defined in 15 this claim; or R3B is CH(R7B)CH2OH wherein R7B has the same significance as defined for R2B in the last instance; or R^{2B} and R^{3B} together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, (4-phenylmethyl)piperidinyl or (4-20 methyl)piperizinyl; with the proviso that when R1B is (lower alkoxycarbonyl) amino then R2B is hydrogen; or a therapeutically acceptable acid addition salt thereof.
- 74. A compound of formula 1b of claim 73 wherein R^{1B} is hydrogen, amino, methylamino, dimethylamino, acetylamino or (1,1-dimethylethoxycarbonyl)amino; R^{2B} is hydrogen, methyl, ethyl, propyl, butyl, 1,1-dimethylethyl, 2-methylpropyl, 2,2-dimethylpropyl, 1-propenyl, 2-propenyl, 2-propynyl, phenylmethyl, 1(R)-phenylethyl, 1(S)2-phenylethyl, 2-phenylethyl,

```
(4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-
        fluorophenyl)methyl, (4-fluorophenyl)methyl, (2-
        hydroxyphenyl) methyl, (4-methoxyphenyl) methyl, (2-
        methylphenyl)methyl, (4-methylphenyl)methyl, {(2-
        trifluoromethoxyphenyl)methyl), (2-hydroxy-3-
 5
        methoxyphenyl)methyl, cyclopropylmethyl,
        cyclopentylmethyl, cyclohexylmethyl, 2-
        cyclohexylethyl, (1-hydroxycyclohexyl)methyl, 2-(4-
        morpholinyl) ethyl, 2-pyridinylmethyl, 3-pyridinyl-
10
        methyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-
        (3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-
        furanylmethyl, 2-thienylmethyl, 3-thienylmethyl, 2-
        thiazolylmethyl, 1-(phenylmethyl)piperidin-4-yl or
       2-benzimidazolylmethyl; R3B is methyl, ethyl,
       propyl, butyl, 1,1-dimethylethyl, 2-methylpropyl,
15
       2,2-dimethylpropyl, phenylmethyl, 2-phenylethyl, (4-
       chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-
       fluorophenyl) methyl, (4-fluorophenyl) methyl, (2-
       hydroxyphenyl)methyl, (4-methoxyphenyl)methyl, (2-
20
       methylphenyl)methyl, (4-methylphenyl)methyl, {(2-
       trifluoromethoxy)phenyl}methyl, (2-hydroxy-3-
       methoxyphenyl)methyl, 1-indanyl, 2-indanyl, cyclo-
       pentylmethyl, cyclohexylmethyl, 2-cyclohexylethyl,
       (1-hydroxycyclohexyl)methyl, 2-(4-morpholinyl)ethyl,
25
       2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinyl-
       methyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl,
       2-(4-pyridinyl)ethyl, 2-thienylmethyl, 3-thienyl-
       methyl, 2-thiazolylmethyl, 1(R)-phenylethyl, 1(S)-
       phenylethyl, 1(R)-cyclohexylethyl or 1(S)-
30
       cyclohexylethyl;
       or R3B is:
```

wherein R^{4B} is hydrogen, methyl, 1-methylethyl, phenylmethyl, cyclohexylmethyl, 3-pyridinylmethyl or (1H-imidazol-4-yl)methyl; R^{5B} has the same significance as defined for R^{2B} in the last instance and R^{6B} has the same significance as defined for R^{3B} in the last instance; or R^{3B} is CH₂CH₂NR^{5B}R^{6B} wherein R^{5B} and ^{6B} are as defined in this claim; or R^{3B} is CH(R^{7B})CH₂OH wherein R^{7B} has the same significance as defined for R^{4B} in the last instance; or a therapeutically acceptable acid addition salt thereof.

A compound of formula 1b of claim 73 is 15 represented by Group 3-formula 1b wherein R1B is hydrogen, amino, methylamino, dimethylamino, acetylamino or (1,1-dimethylethoxycarbonyl)amino; R^{2B} is hydrogen, methyl, ethyl, propyl, butyl, 1,1-20 dimethylethyl, 2-methylpropyl or 2,2-dimethylpropyl; R3B is methyl, ethyl, propyl, butyl, 1,1dimethylethyl, 2-methylpropyl, 2,2-dimethylpropyl, phenylmethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4-25 fluorophenyl)methyl, (2-hydroxyphenyl)methyl, (4methoxyphenyl)methyl, (2-methylphenyl)methyl, (4methylphenyl) methyl, {(2-trifluoromethoxy)phenyl}methyl, (2-hydroxy-3-methoxyphenyl)methyl, 1indanyl, 2-indanyl, cyclopentylmethyl, cyclohexyl-30 methyl, 2-cyclohexylethyl, (1-hydroxycyclohexyl)methyl, 2-(4-morpholinyl)ethyl, 2-pyridinyl-

- 293 -

methyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl, 3-thienylmethyl, 2-thiazolylmethyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 1(R)-cyclohexylethyl or 1(S)-cyclohexylethyl; or R3B is:

wherein R^{4B} is hydrogen, methyl, 1-methylethyl,
phenylmethyl, cyclohexylmethyl, 3-pyridinylmethyl,
or (1H-imidazol-4-yl)methyl; R^{5B} is hydrogen or has
the same significance as defined for R^{3B} in the last
instance and R^{6B} has the same significance as
defined for R^{3B} in the last instance; or R^{3B} is

CH(R^{7B})CH₂OH wherein R^{7B} has the same significance
as defined for R^{4B} in the last instance; or a
therapeutically acceptable acid addition salt
thereof.

20 A compound of formula 1b of claim 73 wherein RlB is hydrogen, amino, methylamino, dimethylamino, acetylamino or (1,1-dimethylethoxycarbonyl)amino; R^{2B} is hydrogen, methyl, ethyl, propyl, butyl, 1,1dimethylethyl, 2-methylpropyl, 2,2-dimethylpropyl, 25 phenylmethyl, 2-phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4fluorophenyl)methyl, (2-hydroxyphenyl)methyl, (4methoxyphenyl) methyl, (2-methylphenyl) methyl, (4methylphenyl)methyl, {(2-trifluoromethoxy)phenyl}methyl, (2-hydroxy-3-methoxyphenyl)methyl, 30 cyclopentylmethyl, cyclohexylmethyl, 2cyclohexylethyl, (1-hydroxycyclohexyl)methyl, 2-(4-

5

morpholinyl) ethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl) ethyl, 2-(3-pyridinyl) ethyl, 2-(4-pyridinyl) ethyl, 2-thienylmethyl, 3-thienylmethyl, 2-thiazolylmethyl, 1(R)-phenylethyl or 1(S)-phenylethyl; and R^{3B} is:

wherein R^{4B} is hydrogen, methyl, 1-methylethyl, phenylmethyl, cyclohexylmethyl, 3-pyridinylmethyl or (1H-imidazol-4-yl)methyl; R^{5B} has the same significance as defined for R^{2B} in this claim and R^{6B} has the same significance as defined for R^{2B} in this claim excluding hydrogen; or R^{3B} is CH(R^{7B})CH₂OH wherein R^{7B} has the same significance as defined for R^{4B} in the last instance; or a therapeutically acceptable acid addition salt thereof.

77. A compound of formula 1b of claim 76 wherein 20 R^{1B} is amino; R^{2B} is hydrogen or phenylmethyl; R^{3B} is:

wherein R^{4B} is hydrogen, R^{5B} is hydrogen or phenylmethyl and R^{6B} is phenylmethyl, 1(R) - phenylethyl or 1(S) -phenylethyl; or R^{3B} is $CH(R^{7B})CH_2OH$ wherein R^{7B} is phenylmethyl and the carbon atom bearing the R^{7B} group has the (S)

configuration; or a therapeutically acceptable acid addition salt thereof.

- 78. A compound of formula 1b of claim 74 wherein

 R1B is amino or (1,1-dimethylethyloxycarbonyl)amino;
 R2B is hydrogen, 2-propynyl, phenylmethyl, 2phenylethyl, cyclopropylmethyl, 2-pyridinylmethyl,
 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(2pyridinyl)ethyl, 2-furanylmethyl, 1(phenylmethyl)piperidin-yl or 2-
- 10 (phenylmethyl)piperidin-yl or 2benzimidazolylmethyl; R^{3B} is phenylmethyl or (3fluorophenyl)methyl;
 or R^{3B} is:

15

20

25

wherein R^{4B} is hydrogen, R^{5B} is hydrogen, methyl, phenylmethyl, (2-hydroxyphenyl)methyl, (2-methylphenyl)methyl, ((2-trifluoromethoxy)phenyl)-methyl, (2-hydroxy-3-methoxyphenyl)methyl, (1-hydroxycyclohexyl)methyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl or 2-thiazolylmethyl; and R^{6B} is phenylmethyl or 1(S or R)-phenylethyl; or R^{3B} is CH₂CH₂NR^{5B}R^{6B} wherein R^{5B} is phenylmethyl and R^{6B} is phenylmethyl or 1(S or R)-phenylethyl; or R^{3B} is CH(R^{7B})CH₂OH wherein R^{7B} is phenylmethyl and the carbon atom bearing the R^{7B} group has the (S) configuration; or a therapeutically acceptable acid addition salt thereof.

79. A compound as defined in claim 73 selected from the group consisting of:

(i) a compound of formula 1b wherein ${\rm R}^{\rm 1B}$ is ${\rm NH_2}$ and ${\rm R}^{\rm 2B}$ and ${\rm R}^{\rm 3B}$ are defined by one of the following combinations:

Combination of R ^{2B} and R ^{3B}		
R2B	R3B	
Н	PhCH ₂	
Н	(3-FPh)CH ₂	
Bu	Bu	
	H ₂ C	
Н	CH ₂ C(O)NHCH ₂ Ph	
H	$CH_2C(O)N(CH_2Ph)_2$	
н .	CH ₂ C(O)NCH ₃	
PhCH ₂	CH ₂ C (O) N CH ₃	

- 297 -

Combination of R ^{2B} and R ^{3B}		
R ^{2B}	R3B	
Н	HC NH CH ₃	
н	HC OH	
Н	HCOH	
PhCH ₂	PhCH ₂	
Me	CH ₂ C(O)N(CH ₂ Ph) ₂	
PhCH ₂	CH ₂ C(0)N(CH ₂ ——N)2	
PhCH ₂	Ch ₂ C(O)N(CH ₂ Ph)CH ₂ —	
PhCH ₂	Ch ₂ C(O)N(CH ₂ Ph)CH ₂ —	
PhCH ₂	CH ₂ C(O)N(CH ₂ Ph)CH ₂ CH ₂ -NO	

- 298 -

Combination of R ^{2B} and R ^{3B}		
R ^{2B}	R3B	
PhCH ₂	CH ₂ C(O)N(CH ₂ Ph)CH ₂ -	
PhCH ₂	CH ₂ C(0)N(CH ₂ Ph)CH ₂	
PhCH ₂	CH ₂ C(O)N(CH ₂ Ph)CH ₂ OH	
NCH ₂	CH ₂ C (O)N (CH ₂ Ph) ₂	
CH ₂	CH ₂ C (O)N (CH ₂ Ph) ₂	
HC≡CCH ₂	$\mathrm{CH_2C}\left(\mathrm{O}\right)\mathrm{N}\left(\mathrm{CH_2Ph}\right)_2$	
PhCH ₂	CH ₂ C(O)N(CH ₂ Ph)CH ₂	
PhCH ₂	F ₃ CO CH ₂ C(O)N(CH ₂ Ph)CH ₂	
PhCH ₂	CH ₂ C(0)N(CH ₂ Ph)CH ₂	

Combination of R ^{2B} and R ^{3B}		
R ^{2B}	R ^{3B}	
PhCH ₂	CH ₂ C (O) N Me	
PhCH ₂	CH ₂ C (O) N Me	
PhCH ₂	CH ₂ C (O) N Me	
PhCH ₂	CH ₂ C(0)N Me	
CH ₂ CH ₂	CH ₂ C(O)N(CH ₂ Ph) ₂	

Combi	nation of R ^{2B} and R ^{3B}
_R 2B	. _R 3B
Ph-(S)-CHMe	CH ₂ C(O)N(CH ₂ Ph) ₂
Ph-(R)-CHMe	CH ₂ C(O)N(CH ₂ Ph) ₂
N H	CH ₂ C (O) N (CH ₂ Ph) ₂
O CH ₂	CH ₂ C(O)N(CH ₂ Ph) ₂
N CH ₂	CH ₂ C(O)N Me
N CH ₂	CH ₂ C(O)N Me

Combination of R ^{2B} and R ^{3B}		
R ^{2B}	R3B	
CH ₂	CH ₂ C (O) N Me	
N CH ₂ CH ₂	CH ₂ C(0)N Me	
Ph- (<i>R</i>) -CHMe	CH ₂ C(O)N Me	
N N H	CH ₂ C (O) N Me	

Combination of R^{2B} and R^{3B}		
R ^{2B}	R3B	
HC≡C-CH ₂	CH ₂ C(O)N Me	
├ —сн₂	CH ₂ C(O)N Me	
PhCH ₂ CH ₂	CH ₂ C(O)NMe	
1-(phenyl- methyl)- piperidin- 4-yl	CH ₂ C(O)N Me	

Con	bination of R ^{2B} and R ^{3B}
_R 2B	R3B
н	CH ₂ C (O) N Me OH OMe
н	CH ₂ C(0)N(CH ₂ Ph)CH ₂ — S
н	CH ₂ C(0)N(CH ₂ Ph)CH ₂
Н	CH ₂ CH ₂ N Me
Н	CH ₂ CH ₂ N(CH ₂ Ph) ₂

Combination of R^{2B} and R^{3B}			
_R 2B	_R 3B		
PhCH ₂	CH ₂ CH ₂ N Me		

5

(ii) and a compound of formula 1b wherein ${\rm R}^{1B},\ {\rm R}^{2B}$ and ${\rm R}^{3B}$ are defined by one of the following combinations:

Combination of R^{1B} , R^{2B} and R^{3B}					
R1B	R ^{2B}	R3B			
Me ₃ COC(O)NH	PhCH ₂	$CH_2C(O)N(CH_2Ph)_2$			
Me ₃ COC(O)NH	PhCH ₂	CH ₂ C (O) N CH ₃			

80. A compound of formula G of claim 1 having the formula 1c:

- wherein R1C is hydrogen, lower alkyl, amino, lower 5 alkylamino, di(lower alkyl)amino, lower alkanoylamino or (lower alkoxycarbonyl)amino; R^{2C} and R^{3C} each independently is hydrogen, lower alkyl, phenyl, phenyl-(1-3C)alkyl or phenyl-(1-3C)alkyl monosubstituted or disubstituted on the aromatic portion 10 thereof with a substituent selected independently from the group consisting of halo, hydroxy, lower alkoxy and lower alkyl; 1-indanyl, diphenylmethyl, lower cycloalkyl, (lower cycloalkyl)-(1-3C)alkyl or (Het)-(1-3C)alkyl wherein Het is as defined in claim 15 1; or a therapeutically acceptable acid addition salt thereof.
- 81. A compound of formula 1c of claim 80 wherein

 R1C is amino, methylamino, acetylamino or (1,1dimethylethoxycarbonyl)amino; R2C and R3C are
 independently hydrogen, methyl, ethyl, propyl,
 butyl, 1,1-dimethylethyl, 2,2-dimethylpropyl,
 phenyl, phenylmethyl, 1(R)- or 1(S)-phenylethyl, 2phenylethyl, (4-(1,1-dimethylethyl)phenyl)methyl,
 (4-chlorophenyl)methyl, (3-fluorophenyl)methyl, (4fluorophenyl)methyl, (4-methoxyphenyl)methyl, 1indanyl, diphenylmethyl, cyclohexyl,
 cyclopentylmethyl, cyclohexylmethyl,
 30 cycloheptylmethyl, 2-cyclohexylethyl, 2-(4-

5

10

morpholinyl)ethyl, 2-pyridinylmethyl, 3pyridinylmethyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl,
2-thienylmethyl or 3-thienylmethyl; or a therapeutically acceptable acid addition salt thereof.

- 82. A compound of formula 1c of claim 81 wherein R^{1C} is amino, R^{2C} is hydrogen or phenylmethyl, and R^{3C} is phenyl, phenylmethyl, 2-phenylethyl, {4-(1,1-dimethylethyl)phenyl}methyl, (3-fluorophenyl)methyl, 1-indanyl, cyclohexyl, cyclohexylmethyl, 2-pyridinylmethyl, 3-pyridinylmethyl or 4-pyridinylmethyl; or a therapeutically acceptable acid addition salt thereof.
- 83. A compound of formula 1c of claim 81 wherein R^{1C} is amino, methylamino or acetylamino, R^{2C} is hydrogen or phenylmethyl, and R^{3C} is phenyl, phenylmethyl, cyclohexyl or cyclohexylmethyl; or a therapeutically acceptable acid addition salt thereof.
 - 84. A compound as defined in claim 81 selected the group consisting of:
- 25 (i) a compound of formula 1c wherein R^{1C} is amino and R^{2C} and R^{3C} are as defined by one of the following combinations:

Comb	inations of R^{2C} and R^{3C}		
R ^{2C}	R ³ C		
H	PhCH ₂		
Н	Сн²		
Н	PhCH ₂ CH ₂		
PhCH-			
Н	N CH ₂		
Me	PhCH ₂		
H	Ph		
н	N CH ₂		
Н	CH ₂		
Н	CH ₂ CH ₂		
H	Ph ₂ CH		
н			
Me	\bigcirc		
Н	(4-Me ₃ CPh)CH ₂		
н	(4-FPh)CH ₂		
H	(4-MeOPh)CH ₂		
H	(3-FPh)CH ₂		

(ii) and a compound of formula 1c wherein R^{1C} , R^{2C} , and R^{3C} are as defined by one of the following combinations:

Combinations	of R1C , R2C,	and R3C
R1C	_R 2C	_R 3C
Me3COC(O)NH	PhCH ₂	PhCH ₂
MeC(O)MH	PhCH ₂	PhCH ₂
NHMe	PhCH ₂	PhCH ₂

85. A compound of formula G of claim 1 having the formula 1d wherein:

5

R^{1D} is hydrogen, lower alkyl, amino, lower alkylamino, di(lower alkylamino), lower alkanoylamino, (lower alkoxycarbonyl)amino or di(lower alkoxycarbonyl)amino; R2D is hydrogen, 10 lower alkyl, phenyl-(1-3C)alkyl, phenyl-(1-3C)alkyl monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; (lower cycloalkyl)-(1-3C)alkyl, or (Het)-(1-3C)alkyl wherein Het is as defined in claim 15 1; and R3D is lower alkyl, lower alkyl monosubstituted, disubstituted or trisubstituted with a halo; phenyl unsubstituted, monosubstituted or disubstituted with a halo, hydroxy, lower alkoxy or lower alkyl; phenyl-(1-3C) alkyl unsubstituted, 20 monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; lower cycloalkyl, (lower cycloalkyl)-(1-3C)alkyl, Het wherein Het is as

defined in this claim, (Het)-(1-3C)alkyl wherein Het is as defined in this claim; lower alkylamino, di(lower alkyl)amino or phenyl-(1-3C)alkylamino unsubstituted, monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; or a therapeutically acceptable acid addition salt thereof.

- 86. A compound of formula 1d of claim 85 wherein R1D is amino, methylamino, dimethylamino, acetylamino, (1,1-dimethylethoxycarbonyl)amino or di(1,1-dimethylethoxycarbonyl)amino; R2D is hydrogen, methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, phenylmethyl, 2-
- phenylethyl, (4-chlorophenyl)methyl, (2-fluorophenyl)methyl, (3-fluorophenyl)methyl, (4-fluorophenyl)methyl, (4-methoxyphenyl)methyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclohexylethyl, 2-(4-morpholinyl)ethyl, 2-pyridinylmethyl, 3-
- pyridinylmethyl, 4-pyridinylmethyl, 2-(2pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4pyridinyl)ethyl, 2-thienylmethyl or 3-thienylmethyl;
 and R^{3D} is methyl, ethyl, propyl, butyl, 2methylpropyl, 2,2-dimethylpropyl, trifluoromethyl,
- phenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-chloro-2methoxyphenyl, phenylmethyl, 2-phenylethyl, (4chlorophenyl)methyl, (2-fluorophenyl)methyl, (3fluorophenyl)methyl, (4-fluorophenyl)methyl, (4-
- 30 methoxyphenyl)methyl, cyclopentyl, cyclohexyl,
 cyclopentylmethyl, cyclohexylmethyl, 2 cyclohexylethyl, 2-pyridinyl, 3-pyridinyl, 4 pyridinyl, 2-thienyl, 3-thienyl, 2-(4 morpholinyl)ethyl, 2-pyridinylmethyl, 3-pyridinyl-

20

thereof.

- methyl, 4-pyridinylmethyl, 2-(2-pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, 2-(4-pyridinyl)ethyl, 2-thienylmethyl, 3-thienylmethyl, methylamino, ethylamino, propylamino, butylamino, (2-
- 5 methylpropyl)amino, (2,2-dimethylpropyl)amino, dimethylamino, diethylamino, dipropylamino, dibutylamino, di(2-methylpropyl)amino, (di(2,2-dimethylpropyl)}amino, (phenylmethyl)amino, (2-phenylethyl)amino, {(4-chlorophenyl)methyl}amino, {(2-
- 10 fluorophenyl)methyl)amino, {(3-fluorophenyl)methyl)amino, {(4-fluorophenyl)methyl)amino, {(4methoxyphenyl)methyl)amino; or a therapeutically
 acceptable acid addition salt thereof.
- 87. A compound of formula 1d of claim 86 wherein R^{1D} is amino; R^{2D} is hydrogen or phenylmethyl; and R^{3D} is phenyl, phenylmethyl, {(4-fluorophenyl)-methyl}amino, cyclohexyl or dibutylamino; or a therapeutically acceptable acid addition salt
 - 88. A compound of formula 1d of claim 86 wherein R^{1D} is amino, (1,1-dimethylethoxycarbonyl)amino or di(1,1-dimethylethoxycarbonyl)amino; R^{2D} is hydrogen
- or phenylmethyl; and R^{3D} is 2,2-dimethylpropyl, trifluoromethyl, phenyl, phenylmethyl, 4-pyridinyl or dibutylamino; or a therapeutically acceptable acid addition salt thereof.
- 30 89. A compound of formula 1d of claim 85 wherein R^{1D} , R^{2D} , and R^{3D} are as defined by one of the following combinations:

- 311 -

Combinations of P1D P2D and P3D					
Combinations of R ^{1D} , R ^{2D} , and R ^{3D}					
RID	R ^{2D}	R3D			
NH ₂	Н	5-Cl-2-MeOPh			
NH ₂	Н	Ph			
NH ₂	H	CF ₃			
NH ₂	н	3-pyridinyl			
NH ₂	H	PhCH ₂			
NH ₂	н	Me ₃ CCH ₂			
NH ₂	Н	Me ₃ CO			
NH ₂	н	(4-FPh)CH2NH			
NH ₂	н	Bu ₂ N			
NH ₂	PhCH ₂	Ph			
NH ₂	PhCH ₂				
NH ₂	PhCH ₂	4-pyridinyl			
NH ₂	PhCH ₂	CF ₃			
(Me ₃ COC(O)) ₂ N	Н	Ph			
NH ₂	PhCH ₂	PhCH ₂			
Me ₃ COC(O)NH	H	Bu ₂ N			
Me ₃ COC(O)NH	PhCH ₂	Ph			
Me ₃ COC(O) ₂ N	PhCH ₂	Ph			

- 90. A process for preparing a compound of formula G as defined in claim 1, or a therapeutically acceptable addition salt therof, selected from the group consisting of the following processes I to V:
 - (I) A process for preparing a compound of formula G represented by formula 1

$$R^{1}$$
 R^{1}
 R^{1}
 R^{1}
 R^{1}
 R^{2}
 R^{2}
 R^{3}
 R^{2}
 R^{2}
 R^{3}
 R^{2}
 R^{3}
 R^{4}

wherein R^1 has the same significance as R in claim 1 and R^2 , R^3 , R^4 , R^5 and Q are as defined as claim 1, comprising:

(a) coupling a thiazolylaniline of the formula

wherein \mathbb{R}^1 and \mathbb{R}^2 are as defined in this claim with an amino acid derivative of the formula

10

wherein R³, R⁵ and Q are as defined in this claim and R^{4AA} is an amino protecting group or a radical as defined for R⁴ in claim 1 other than hydrogen to obtain a corresponding aminoamide of the formula

and, when R^{4AA} has the same significance as R⁴ as defined in claim 1 but excluding hydrogen, the 20 aminoamide so obtained is a corresponding compound of formula 1 wherein R⁴ is other than hydrogen; and,

when R^{4A} of the amidoamide so obtained is a amino protecting group, the latter aminoamide is deprotected to give the corresponding compound of formula 1 wherein R^4 is hydrogen; or

(b)(i) reacting a methylketone of the formula

Me (0) C

NHC (0) -Q-CH (
$$\mathbb{R}^3$$
) -N- \mathbb{R}^5

5

25

wherein R³, R^{4AA}, R⁵ and Q are as defined in this local claim with thiourea and iodine to obtain the corresponding aminothiazole of derivative of the formula

and, when R^{4AA} has the same significance as R⁴ as defined in claim 1 but excluding hydrogen, the aminothiazole derivative so obtained is the corresponding compound of formula 1 wherein R¹ is amino, R² is hydrogen, R⁵ and Q are as defined in this claim, and R⁴ is other than hydrogen; and when R^{4A} of the aminothiazole derivative so obtained is an amino protecting group, the latter derivative is deprotected to give the corresponding compound of formula 1 wherein R⁴ is hydrogen; or

(b)(ii) N-alkylating the aforementioned methyl ketone with a lower alkyl bromide, chloride or

iodide to obtain the corresponding N-alkylated derivative of the formula

wherein R^{2A} is lower alkyl, reacting the Nalkylated derivative with thiourea and iodine, followed by removing any amino protecting group if required, to obtain the corresponding compound of formula 1 wherein R² is lower alkyl; or

10

(c) reacting a bromoacetamide of the formula

15 wherein PG is an amino protecting group with an appropriate primary or secondary amine to obtain the corresponding intermediate of the formula

and removing the protecting group PG from the latter intermediate to obtain the corresponding compound of formula 1 wherein R^1 is amino, R^2 and R^3 each is hydrogen, and R^4 and R^5 are as defined in this claim and Q is absent; or

> (d)(i) reacting the methyl ketone of formula

5

10

wherein R^{4BB} has the same significance as R^4 as defined in this claim but excluding hydrogen and R^{5BB} has the same significance as R^{5} defined herein, with thiourea and iodine to give a corresponding compound of formula 1 wherein ${\bf R}^1$ is amino, ${\bf R}^2$ and ${\bf R}^3$ each is hydrogen, R^4 is as defined in this claim but excluding hydrogen \mathbb{R}^5 as defined in this claim and \mathbb{Q} is methylene; or

(d)(ii) protecting the inherent secondary amide 15 of the preceding methyl ketone wherein R^{4BB} is hydrogen with an amino protecting group to obtain the corresponding amino protected derivative of the formula

20

25

wherein R5BB and PG are as defined in this claim; reacting the latter derivative with thiourea and iodine, whereby the amino protecting group cleaved in situ and the corresponding aminothiazole compound of formula 1 wherein R^1 is amino, R^2 , R^3 and R^4 each is hydrogen, R^5 is as defined in this claim and Q is methylene is obtained;

and if desired, effecting standard transformations of the products of processes (b)(i), (b)(ii), (c), 30

(d)(i) or (d)(ii) to obtain other compounds of formula 1;

and further, if desired, converting the compound of formula 1 into a therapeutically acid addition salt.

(II) A process for preparing a compound of formula G represented by formula 1a

$$R^{1A} \xrightarrow{N} O \xrightarrow{R^{2A}} R^{3A}$$

$$0 \xrightarrow{R^{4A}} R^{4A}$$

$$(1a)$$

wherein R^{1A} has the same meaning as R in claim 1 and R^{2A} , A, R^{3A} and R^{4A} are as defined in claim 1, comprising:

(a) reacting in the presence of N, N'-carbonyldiimidazole a compound of the formula

wherein R^{1AA} is hydrogen, lower alkyl, (amino protecting group)-amino, (amino protecting group)-(lower alkylamino) or di(lower alkyl)amino and R^{2A} is hydrogen or lower alkyl, with an amine of the formula:

5

wherein R^{3A} and R^{4A} are as defined in claim 1; and, if required, eliminating from the instant product any protective groups, and effecting standard transformations; to obtain the corresponding compound of formula 1a wherein A is absent and R^{1A}, R^{2A}, R^{3A} and R^{4A} are as defined in claim 1; or

(b) reacting an isocyanate of formula:

10 with an amine of formula:

$$HN < R^{3A}$$

wherein R^{3A} and R^{4A} are as defined in claim 1, to obtain the corresponding ureido derivative of formula:

and either (i) reacting the ureido derivative with a thiourea derivative of the formula H₂N-C(S)-R¹BB, wherein R¹BB is amino, lower alkylamino or di(lower alkyl)amino, and a halogen, selected from Br₂, Cl₂ or I₂, to obtain the corresponding compound of formula 1a wherein R¹A is amino, lower alkylamino or

di(lower alkyl)amino, R^{2A} is hydrogen, A is absent and R^{3A} and R^{4A} are as defined in claim 1; or (ii) reacting the latter ureido derivative with Br₂, Cl₂ or I₂ whereby the methyl ketone moiety of the ureido derivative is converted to a haloketone moiety, to give the corresponding α -haloketone, and reacting the α -haloketone with a thioamide of the formula H_2N -C(S)-R¹CC wherein R¹CC is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino to obtain the corresponding compound of formula 1a wherein R¹A is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino, R^{2A} is hydrogen, A is absent and R^{3A} and R^{4A} are as defined in claim 1;

15 and, if required, eliminating from the instant product of (i) or (ii) any protective groups, and effecting standard transformations to obtain the corresponding compound of formula la wherein A is absent, R^{1A}, R^{3A} and R^{4A} are as defined in claim 1 and R^{2A} is hydrogen; or

(c) reacting a compound of the formula:

$$H_2N$$
 S
 H_2N
 CH_3
 CH_3

with an amine of the formula:

25

- 319 -

wherein R^{3A} and R^{4A} are as defined in claim 1, to obtain the corresponding compound of formula 1a wherein R^{1A} is amino, R^{2A} is hydrogen, A is absent and R^{3A} and R^{4A} are as defined in claim 1; or

5

20

(d) reacting a compound of the formula:

wherein R^{1A} and R^{2A} are as defined in claim 1 with a reagent of the formula:

wherein R^{3A} and R^{4A} are as defined in claim 1, to obtain the corresponding compound of formula 1a wherein A is carbonyl and R^{1A}, R^{2A}, R^{3A} and R^{4A} are as defined in claim 1;

and if desired, effecting standard transformations

15 to the products of the last named processes (a),

(b), (c) and (d) to obtain other compounds of formula la;

and further, if desired, converting the compound of formula la into a therapeutically acceptable acid addition salt.

(III) A process for preparing a compound of formula G represented by formula 1b:

5

wherein R1B has the same significance as R in claim 1, and R^{2B} and R^{3B} are as defined in claim 1, comprising:

10

(a) coupling a compound of the formula

wherein R1B is as defined in this claim, with an 15

amine of the formula:

wherein R^{2B} and R^{3B} are as defined in this claim, to obtain the corresponding compound of formula 1b; or

20

(b) coupling 4-acetylbenzoic acid with an amine of the formula:

wherein R^{2B} and R^{3B} are as defined in this claim, to obtain the corresponding benzamide derivative of the formula:

5

and either (i) reacting the latter benzamide derivative with Br_2 , Cl_2 or I_2 whereby the methyl ketone moiety of the benzamide derivative is converted to the corresponding α -haloketone and reacting the resulting α -haloketone with a 10 thioamide or thiourea of the formula $H_2N-C(S)-R^{1AAA}$ wherein RlAAA is hydrogen, lower alkyl, amino, lower alkylamino or di(lower alkyl)amino to obtain the corresponding compound of formula 1b wherein R^{1B} is hydrogen, lower alkyl, amino, lower alkylamino or 15 di(lower alkyl)amino, and R^{2B} and R^{3B} are as defined in this claim; or (ii) reacting the latter benzamide derivative with a thiourea derivative of the formula $H_2N-C(S)-R^{1AAA}$, wherein R^{1AAA} is amino, lower

- alkylamino or di(lower alkyl)amino, in the presence of Br₂, Cl₂ or I₂ to obtain the corresponding compound of formula 1b wherein R^{1B} is amino, lower alkylamino or di(lower alkyl)amino and R^{2B} and R^{3B} are as defined in this claim;
- and if desired, effecting standard transformations to the products of the last named processes (a) and (b) to obtain other compounds of formula 1b; and further, if desired, converting the compound of formula 1b into a therapeutically acceptable acid addition salt.

(IV) A process for preparing a compound of formula G represented by formula 1c

5 wherein R^{1C} has the same significance as R in claim 1 and R^{2C} and R^{3C} are as defined in claim 1, comprising:

coupling a thiazolylphenoxyacetic acid of the 10 formula

wherein R^{1} is as defined in this claim with a primary or secondary amine of the formula

wherein R^{2C} and R^{3C} are as defined in this claim to give the corresponding compound of formula 1c wherein R^{1C}, R^{2C} and R^{3C} are as defined in this claim; and, if desired, converting the compound of formula 1c into a therapeutically acceptable salt thereof.

WO 97/24343 PCT/US96/19131

(V) A process for preparing a compound of formula G represented by formula 1d

5

wherein R^{1D} has the same significance as R in claim 1, and R^{2D} and R^{3D} are as defined in claim 1, comprising:

(a) coupling a 4-thiazolylphenyl derivative of the formula

$$\mathbb{R}^{\frac{1D}{S}} \stackrel{\mathbb{N}}{\longrightarrow} \mathbb{N}$$

- wherein R^{1D} is as defined in this claim with a carboxylic acid derivative of the formula R^{3DA} COOH wherein R^{3DA} is lower alkyl, lower alkyl monosubstituted, disubstituted or trisubstituted with a halo; phenyl unsubstituted, monosubstituted or disubstituted with a halo, hydroxy, lower alkoxy or lower alkyl; phenyl(lower alkyl) unsubstituted, monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; lower cycloalkyl, (lower cycloalkyl)-(lower alkyl), Het
 - 324 -

wherein Het is as defined in claim 1, or (Het)-(lower alkyl) wherein Het is as defined in claim 1; to give the corresponding amide derivative of the formula

5

which is a compound of formula 1d in which R^{1D} is as defined in this claim, R^{2D} is hydrogen and R^{3DA} as defined in this claim; or

10

reacting the carbamate derivative of the formula

in which R^{1D} is as defined in this claim with an amine of formula $NR^{4D}R^{5D}$ wherein R^{4D} is hydrogen or lower alkyl and R^{5D} is lower alkyl or phenyl lower alkyl unsubstituted, or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl to give the corresponding 20 ureido derivative of the formula

WO 97/24343 PCT/US96/19131

which is a compound of formula 1d in which R^{1D} is as defined in this claim; R^{2D} is hydrogen and R^{3D} is lower alkylamino, di(lower alkyl)amino, or phenyl-(lower alkyl)amino unsubstituted, monosubstituted or disubstituted on the aromatic portion thereof with a halo, hydroxy, lower alkoxy or lower alkyl; and if desired, effecting standard transformations to the products of the last named processes (a) and (b) to obtain other compounds of formula 1d; and further, if desired, converting the compound of formula 1d into a therapeutically acceptable acid addition salt.

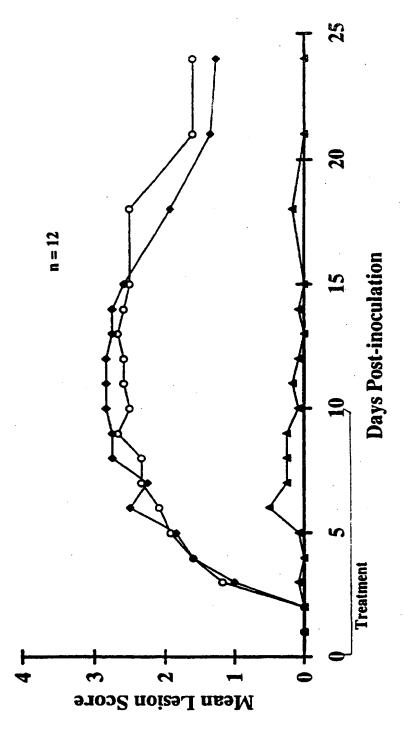
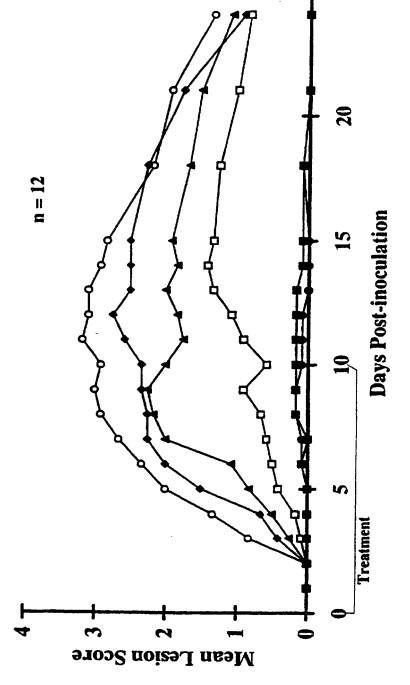
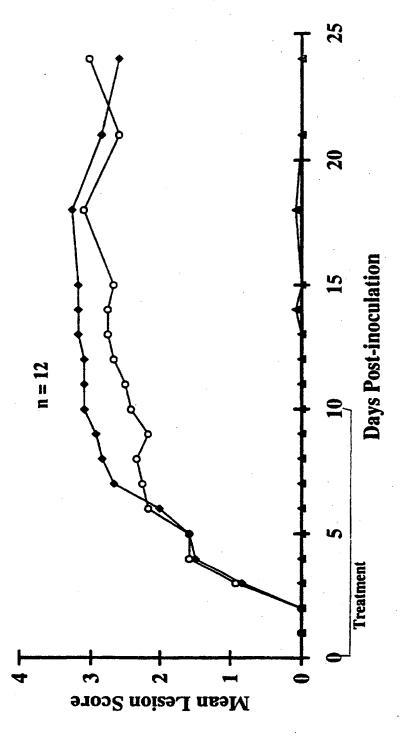


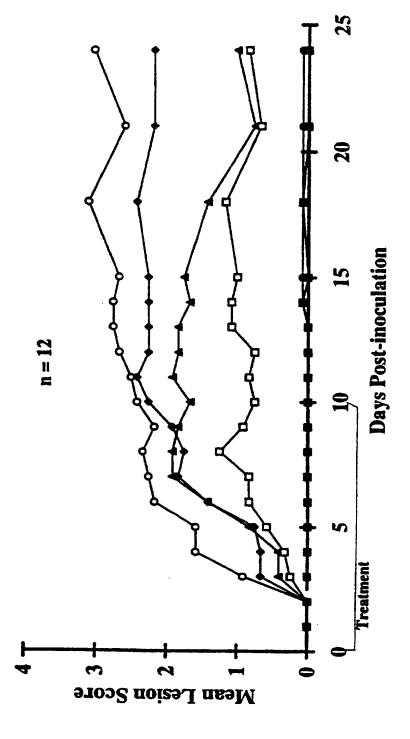
Figure 1



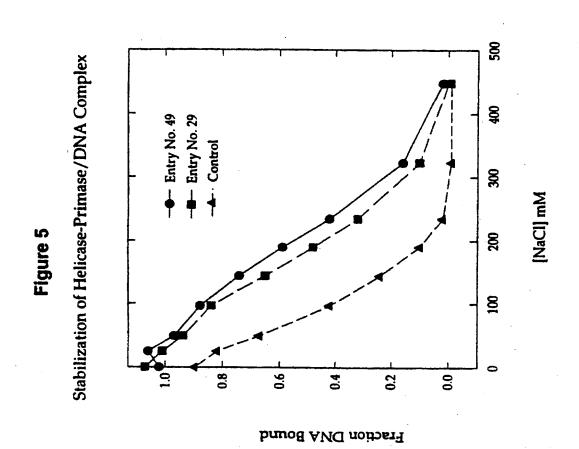
Figure



igure 3



Figure



SUBSTITUTE SHEET (RULE 26)

Internatic . Application No PCT/US 96/19131

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D277/40 A61K31/425 C07D417/14 C07D277/28 C07D417/12 CO7D277/24 CO7D277/30 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) C07D A61K IPC 6 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages Category ' 1 PATENT ABSTRACTS OF JAPAN X vol. 12, no. 283 (C-518), 3 August 1988 & JP 63 060978 A (YOSHITOMI) cited in the application Relevant for Group 5 see abstract 1 BIOORG.MED.CHEM. P,A vol. 4, no. 5, 1996, pages 645-654, XP000653770 SELWAY ET AL: "Parallel-Compound Synthesis: Methodology for Accelerating Drug Discovery" For Group 5 compounds see page 646, column 2 -/--Patent family members are listed in annex. Further documents are listed in the continuation of box C. X "I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the * Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "Y" document of particular relevance; the claimed invention cannot be considered to involve an invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "O" document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of mailing of the international search report Date of the actual completion of the international search 09.06.97 5 May 1997 Authorized officer Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentiaan 2 NL - 2280 HV Ripwijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016

Gettins, M

Internation — Application No
PCT/US 96/19131

	TO THE PROPERTY OF THE PROPERT	LC1/02 30/13131		
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Category '	Clason of document, with interesting, where appropriate, of the recent passages			
A	WO 95 32710 A (MERCK & CO INC ;HARTMAN GEORGE D (US); DUGGAN MARK E (US); IHLE NA) 7 December 1995 cited in the application Group 3	1		
A	GB 2 276 164 A (GLAXO GROUP LTD) 21 September 1994 cited in the application Group 1,3	1		
A	EP 0 545 376 A (FUJISAWA PHARMACEUTICAL CO) 9 June 1993 cited in the application Group 5	1		
A	EP 0 458 037 A (AMERICAN CYANAMID CO) 27 November 1991 cited in the application Groups 1,2,3,4	1		
A	FR 2 656 610 A (SANOFI SA) 5 July 1991 cited in the application Group 1	1		
A	EP 0 372 776 A (PFIZER) 13 June 1990 cited in the application Group 5	. 1		
A	EP 0 279 598 A (PFIZER) 24 August 1988 cited in the application Group 5	1		
A	US 4 746 669 A (CALDWELL CHARLES G ET AL) 24 May 1988 cited in the application Groups 1,2,3	1		
		·		

Information on patent family members

International Application No
PCT/US 96/19131

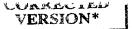
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9532710 A	07-12-95	AU 2586895 A CA 2190870 A EP 0760658 A	21-12-95 07-12-95 12-03-97
GB 2276164 A	21-09-94	NONE	
EP 0545376 A	09-06-93	AU 666893 B AU 2983792 A CA 2084640 A CN 1079469 A HU 65776 A HU 9500396 A JP 2531329 B JP 6321921 A US 5532258 A ZA 9208876 A	29-02-96 10-06-93 07-06-93 15-12-93 28-07-94 28-09-95 04-09-96 22-11-94 02-07-96 15-07-93
EP 0458037 A	27-11-91	US 5128351 A AU 639325 B AU 7607691 A CA 2041687 A CN 1056494 A JP 6001765 A US 5350759 A US 5432189 A US 5225425 A	07-07-92 22-07-93 07-11-91 05-11-91 27-11-91 11-01-94 27-09-94 11-07-95 06-07-93
FR 2656610 A	05-07-91	AT 119160 T AU 627103 B AU 7055591 A CA 2046883 A CN 1053064 A,B CZ 9006277 A DE 69017443 D DE 69017443 T EP 0462264 A ES 2069276 T FI 95380 B WO 9109857 A IE 67322 B	15-03-95 13-08-92 24-07-91 30-06-91 17-07-91 17-01-96 06-04-95 12-10-95 27-12-91 01-05-95 13-10-95 11-07-91 20-03-96

information on patent family members

International Application No
PCT/US 96/19131

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2656610 A		IL 96811 A JP 4504863 T NO 179975 B PL 167101 B RU 2049784 C US 5470855 A	15-03-95 27-08-92 14-10-96 31-07-95 10-12-95 28-11-95
EP 0372776 A	13-06-90	W0 9006303 A AT 143366 T CA 2004249 A,C DE 68927254 D DE 68927254 T ES 2092475 T FI 95465 B IL 92466 A JP 2275853 A JP 7010850 B N0 175257 B PT 92468 B US 5153206 A US 5294619 A	14-06-90 15-10-96 02-06-90 31-10-96 06-02-97 01-12-96 31-10-95 27-02-94 09-11-90 08-02-95 13-06-94 18-07-95 06-10-92 15-03-94
EP 0279598 A	24-08-88	AP 88 A CA 1312080 A CS 8800964 A DE 3884007 D DE 3884007 T DK 170878 B EG 18635 A ES 2058249 T IE 61258 B JP 6099405 B JP 63216875 A SU 1634136 A	06-06-90 29-12-92 11-04-90 21-10-93 20-01-94 26-02-96 30-04-94 01-11-94 19-10-94 07-12-94 09-09-88 07-03-91
US 4746669 A	24-05-88	NONE	

THIS PAGE BLANK (USPTO)



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: C07D 277/40, A61K 31/425, C07D

417/12, 417/14, 277/28, 277/30, 277/24

(11) International Publication Number:

(43) International Publication Date:

WO 97/24343

10 July 1997 (10.07.97)

(21) International Application Number:

PCT/US96/19131

A1

(22) International Filing Date:

4 December 1996 (04.12.96)

(30) Priority Data:

60/009,433 60/023.209 29 December 1995 (29.12.95) US

2 August 1996 (02.08.96)

(71) Applicants: BOEHRINGER INGELHEIM PHARMACEUTI-CALS, INC. [US/US]; 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US). BOEHRINGER INGELHEIM (CANADA) LTD. [CA/CA]; 2100, rue Cunard, Laval, Quebec H7S 2G5 (CA).

(74) Agents: RAYMOND, Robert et al.; Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA. GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PHENYL THIAZOLE DERIVATIVES WITH ANTI HERPES VIRUS PROPERTIES

(57) Abstract

This invention relates to methods for inhibiting herpes replication and for treating herpes infection in a mammal by inhibiting the herpes helicaseprimase enzyme complex. This invention also relates to thiazolylphenyl derivatives of formula (G) that inhibit the herpes helicase-primase and to pharmaceutical compositions comprising the thiazolylphenyl derivatives, to methods of using and methods of producing the thiazolylphenyl derivatives. In formula (G), R and Z are as defined in the application where Z is the characterising feature.

$$R = N$$

$$S$$

$$(G)$$

* (Referred to in PCT Gazette No. 43/1997, Section II)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

Armenia	GB	United Kingdom	MW	Malawi
Austria	GE	Georgia	MX	Mexico
Australia	GN	Guinea	NE	Niger
Barbados	GR	Greece	NL	Netherlands
	HU	Hungary	NO	Norway
	IE	Ireland	NZ	New Zealand
	IT	Italy	PL	Poland
_	JP	Japan	PT	Portugal
	KE	Келуа	RO	Romania
	KG	Kyrgystan	RU	Russian Federation
- -	KP	Democrate ple's Republic	SD	Sudan
		of Korea	SE	Sweden
· ·	KR	Republic ca	SG	Singapore
<u> </u>	KZ	Kazakhsts	SI	Slovenia
	LI	Liechtenst	SK	Slovakia
	LK	Sri Lanka	SN	Senegal
	LR	Liberia	SZ	Swaziland
	LT	Lithuania	TD	Chad
	I.U	Luxembourg	TG	Togo
	LV	Latvia	ŦJ	Tajikistan
•	MC	Monaco	TT	Trinidad and Tobago
	MD	Republic of Moldova	UA	Ukraine
	MG	-	UG	Uganda
· •	ML	Mali	US	United States of America
	MN	Mongolia	UZ	Uzbekistan
	MR	Mauritania	VN	Viet Nam
	Austria Australia	Austria GE Australia GN Barbados GR Belgium HU Burkina Faso IE Bulgaria IT Benin JP Brazil KE Belarus KG Canada KP Central African Republic Congo KR Switzerland KZ Côte d'Ivoire LI Cameroon LK China LR Czechoslovakia LT Czech Republic ILU Germany LV Denmark MC Estonia MD Spain MG Finland ML France MN	Austria GE Georgia Australia GN Guinea Barbados GR Greece Belgium HU Hungary Burkina Faso IE Ireland Bulgaria IT Italy Benin JP Japan Brazil KE Kenya Belarus KG Kyrgystan Canada KP Democrati ple's Republic contral African Republic Contral African Republic Contral African KE KZ Kazakhsts Cote d'Ivoire LI Liechtenst Cameroon LK Sri Lanka China LR Liberia Czechoslovakia LT Lithuania Czech Republic Germany LV Latvia Denmark MC Monaco Estonia MD Republic of Moldova Spain MG Madagascar Finland ML Mali France	Austria GE Georgia MX Australia GN Guinea NE Barbados GR Greece NL Belgium HU Hungary NO Burkina Faso IE Ireland NZ Bulgaria IT Italy PL Benin JP Japan PT Brazil KE Kenya RO Belarus KG Kyrgystan RU Canada KP Democrati ple's Republic SD Central African Republic of Korea SE Congo KR Republic LI Liechtenst SK Cameroon LK Sri Lanka SN China LR Liberia SZ Czechos lovakia LT Lithuania TD Czech Republic LV Laivin TJ Denmark MC Monaco TT Estonia MD Republic of Moldova UA Spain MN Mongolia LV Latina France MN Mongolia LV LV France